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MARCH, 1950

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THE CHEMICAL SOCIETY

SCIENTIFIC MEETINGS DURING MAY, 1950.

LONDON.

Thursday, May 4th, 1950, at 7.15 p.m.

Tilden Lecture, **Recent Advances in the Chemistry of the Steroids,** by Professor F. S. Spring, D.Sc., F.R.I.C.

To be given at the Royal Institution, Albemarle Street, W.1.

BIRMINGHAM.

Friday, May 12th, 1950, at 4.30 p.m.

Lecture, **The Shape of a Chemical Bond,** by Professor C. A. Coulson, M.A., D.Sc.

Joint meeting with the University Chemical Society, to be held in the Main Chemistry Lecture Theatre, The University, Edgbaston, Birmingham.

(*Note :* This date has been changed from May 5th.)

NORTH WALES.

Thursday, May 4th, 1950, at 5.30 p.m.

Lecture, **Light-scattering and Chemistry,** by Dr. E. J. Bowen, M.A., F.R.S.

Joint meeting with University College of North Wales Chemical Society to be held in the Department of Chemistry, University College of North Wales, Bangor.

OXFORD.

Monday, May 1st, 1950, at 8.15 p.m.

Alembic Club Lecture, **The Biochemistry of Fluoroacetate Poisoning and its Significance,** by Professor A. R. Peters, M.C., M.A., F.R.S.

To be given in the Physical Chemistry Laboratory, Oxford. All Fellows are invited.

Monday, May 15th, 1950, at 8.15 p.m.

Alembic Club Lecture, **Some Problems in the Chemistry of Starch and Glycogen,** by Professor E. L. Hirst, D.Sc., F.R.S.

To be given in the Physical Chemistry Laboratory, Oxford. All Fellows are invited.

SOUTHAMPTON.

Friday, May 5th, 1950, at 5 p.m.

Lecture, **Recent Synthetical Developments in Pyrethrum Chemistry,** by Dr. S. H. Harper, A.R.C.S.

Joint meeting with University College of Southampton Chemical Society to be held in the Physics Department, University College, Southampton.

PROCEEDINGS
OF THE
CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held in the Main Chemical Lecture Theatre of the University, Edgbaston, Birmingham, on Friday, February 10th, 1950, at 4.30 p.m.

The President, SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S., was in the Chair.

Opening the meeting, the President expressed his pleasure in taking the Chair at an Official Meeting of the Society in Birmingham. He also conveyed the cordial thanks of the Officers and himself to the University.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: L. L. Bircumshaw, Harold C. Smith, James C. Robb, Hamish R. Cooper, John C. Bevington, P. Cowley, Leslie Valentine, Norman Grassie, L. F. Thomas, F. M. Tayler, L. F. J. Parker, Marjorie L. Hilton, W. M. Corbett, R. P. Smith, H. J. Yardley, K. W. Somerton, C. T. Greenwood, B. H. Newman, A. B. Foster, S. Laland, K. Butler, F. Shafizadeh, D. A. Higgins, W. J. M. Philpott, K. S. Barclay.

LECTURE.

The President delivered a lecture entitled, "Fifty Years of Organic Chemistry." At the conclusion of the address, Sir Norman Haworth proposed a vote of thanks to the President which was carried with acclamation.

Minutes of a

SCIENTIFIC MEETING

held in the Lecture Hall of the Institution of Mechanical Engineers, Storey's Gate, S.W.1, on Thursday, February 16th, 1950, at 7.15 p.m.

The President, SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S., was in the Chair.

MINUTES.

The Minutes of the Scientific Meetings held at Burlington House on February 2nd, and at the University of Birmingham on February 10th, 1950, were read, and were confirmed and signed.

APPOINTMENT OF SCRUTATORS.

Mr. M. F. Ansell and Mr. M. J. Birchenough were appointed Scrutators for the ballot for the election of a Vice-President, who has not filled the Office of President, and Elected Ordinary Members of Council.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: Eileen Blackall, Katherine East, Walter H. Lee, Herchel Smith, Alan Fowler Williams.

PEDLER LECTURE.

After a brief introduction the President called upon Professor J. W. Cook, F.R.S., to deliver the Pedler Lecture entitled, "Polycyclic Aromatic Hydrocarbons." At the conclusion of the lecture, a vote of thanks to the Lecturer, proposed by Sir John Simonsen, was carried with acclamation.

Minutes of a

SCIENTIFIC MEETING

held in the Main Chemistry Lecture Theatre of The Imperial College of Science and Technology, S.W.7, on March 2nd, 1950, at 7.15 p.m.

The President, SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S., was in the Chair.

MINUTES.

The Minutes of the Scientific Meeting held at the Institution of Mechanical Engineers, Storey's Gate, S.W.1, on February 16th, 1950, were read, and were confirmed and signed.

VACANCIES OF COUNCIL 1950.

A list of the nominations received for vacancies on Council 1950 was read.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: Alec Webster, S. F. Brailsford, Peter Wade, D. A. A. Kidd, B. Bannister, C. T. Blood, Cecil L. Leese, K. R. Bharucha, C. C. J. Culvenor, J. A. Coles, H. J. Cottrell, F. P. Doyle.

CENTENARY LECTURE.

After a brief introduction the President called upon Professor Dr. Pl. A. Plattner to deliver the Centenary Lecture entitled "The Azulenes." The lecture was followed by a discussion, and a vote of thanks to the Lecturer, proposed by Professor R. P. Linstead, was carried with acclamation.

OFFICIAL ANNOUNCEMENTS

DEATHS.

The Council regret to announce the deaths of the following Fellows:

	Elected.	Died.
Charles Samuel Bedford (Ripon)	Dec. 7th, 1916.	Nov. 23rd, 1949.
Charles Lester Gabriel (Philadelphia, Pa.)	May 20th, 1943.	November, 1949.
Sir (Edmund) Vivian Gabriel (New York)	Feb. 16th, 1899.	Feb. 15th, 1950.
James MacLeod (Glasgow).....	May 4th, 1899.	Nov 18th, 1949.
Sydney Walter Morris (Barking)	Feb. 20th, 1919.	Nov. 28th, 1949.

CONGRATULATIONS.

The President has conveyed the congratulations of the Council to the following Fellows who completed 60 years of Fellowship on February 6th, 1950:

Sydney Hoare Collins (Worthing).
Edward Russell (Bristol).

and to the following who completed 50 years of Fellowship on February 15th, 1950:

Alexander Hutcheon Bennett (E.C.3).
Alexander Findlay (Beckenham).
Alan Wilfrid Menzies (New Jersey, U.S.A.).
Edgar Ford Morris (Surbiton).

ELECTION OF NEW FELLOWS.

The following 213 candidates were elected Fellows of the Society on February 16th, 1950:

William Eric Addison.
John Alan Alexander.
Ernest James Alford.
Alan James Anderson.
William Anderson.
Raymond Cecil Asher.
Robert Oldham Atkinson.
John Walter Babbs.
John Martyn Bailey.
Thomas Arthur Banfield.
William Arthur Shute Barbour.
John Herbert Barnes.
Cyril Peter Barry
Herbert Geoffrey Charles Bates.
Brian Batterbee.
Vladimir Bazant.
Frederick Walter Beech.
Charles Otto Beckmann.
Donald Peter Benton.
Lionel Frederick Bernamont.
Kekhusroo Rustomji Bharucha.
Malcolm Hugh Blair-McGuffie.
Cyril Thomas Blood.
John Bernard Bookey.
Robert Alwyn Bottomley.
Leslie Bradford.
William Ewart Braybrooks.
Donald Frederick Broadbridge.
Donald Douglas Brown.
John Watson Brown.
Joseph Frederick Bunnett.
Dennis Caldwell.
Tod Wildy Campbell.
John Fulton Carson, jun.
John Cast.
Marco Antonio Cecchini.
Ronald John Christmas.
John William Clark-Lewis.
John Alexander Coles.
Joseph Walters Corse.
Donald J. Cram.
Ernest George Cummins.
Arnold Craig Cuthbertson.
James Joseph Daly.
Hyp Joseph Dauben, jun.
William Garfield Dauben.
Lewis Maldwyn Davies.
Donald West Davidson.
Boyce Ian David Davis.
Jack Davis.
John Edward Davis.
Stanley Joseph Davis.
Peter Alan Dent.
Leslie Creighton Dick.
Raymond M. Dodson.
Frank Peter Doyle.
Kenneth Douglas Drakeley.
David Geoffrey Elias.
John Gwynant Evans.
Gordon James Faulkner.
Thomas Edward Fletcher.
Leslie Harry Ford.
Borivoj Richard Simon Franko-Filipasic.
Charles Aubrey Friedmann.
Mrs. Betsy Morse Friess.
William David Garden.
Theodore Albert Geisman.
Samuel Michael Gerbert.
Brian Montague Gibbs.
John James Gledhill.
Harry Goddard.
Allan P. Gray.
Roy Reginald Gunton.
Michael Geoffrey Hall.
George Gerrard Halliday.
Robert Halstead.
Douglas Harrison.
Margaret Harte.
Ernest Alfred Harvey.
Alwyn Aubrey Haslam.
Donal Herbert Hayes.
Edith Erna Heilpern.
Fritz Jacob Hermann.
James Arnot Horn.
Eric Housley.
Brian Keith Howe.
David Moore Howell.
Donald Albert Howes.
Joseph Ephraim Ho-Yen.
Lloyd Lewis Ingraham.
Michael David Jesse Isaacs.
Doreen Ismay.
Frank Pace Johnson.
John Terrence George Johnson.
William Summer Johnson.
David Morris Jones.
Norman Frederick Kies.
Norman Percival King.
Jozsef Kiss.
Henry Marcell Kissman.
Edwin Coulthard Knight.
Joszef Kovacs.
Hans Konrad Krüsi.
Walter Edward Laird.
Arnold Cooper Lee.
Henry Ramsden Lee.
Walter Lee.
Cecil Leslie Leese.
Alfredo Levy.
Donald George Lewis.
Reginald Norman Lewis.
Michael George Lines.
Frederick Lishman.
Anthony Blair Littlewood.
Agnes Lothian.
Martin Lovett.
John Martin Lowenstein.
Eric Royle Lynch.
Sybil Bridget Roche Lynch.
Bernard John Lyons.
Jeremiah Patrick McCarthy.
John Archibald McEwan.
James Eric McIntyre.
Kenneth Erskine Macphee.
William Denis Maniece.
Lewis Theodore Mann.
Stanley Frederic Marrian.
George Reginald Marshall.

Herbert Meisiich.
Alexander Marshall Meston.
Victor Bernard Meyer.
Brian Beard Millward.
Carl Mathew Moser.
James Murray.
Samuel Martin Nelson.
Melvin Spencer Newman.
Stanley Newton.
Hakon Nord.
John O'Neill.
Raymond George Douglas Osmond.
Clifford Alfred Owen.
Robert Kenneth Packer.
David Lord Pain.
Dennis Vernon Parke.
Kenneth John Parker.
Albert Keith Parsons.
Roy Paulson.
Alan George Pendleton.
Glyn Owain Phillips.
Geoffrey Russell Philpot.
Jack Pickthall.
Stanley John Pirt.
Carl Albert Pitha.
Ervin Garrison Pritchett.
Michael David Ranken.
Returi Bhaskara Rao.
Benjamin Max Ratner.
Allan Arthur Rea.
Frank Reginald Rich.
Alan James Eckersley Rigby.
Royston Murphy Roberts.
Donald Robinson.
Edgar Robert Rogier.
William Raymond Ruby.
David Ruxton.
Hans Eduard Schmid.
William Sharpe.
Norman Sheppard.
Harold Silman.
Edward John Skerrett.
Henry Alistair Skinner.
Harry Lovell Slates.
Meyer Sletzinger.
Norman James Herbert Small.
Peter Smith.
Oscar Vincent Soane.
Anthony William Somerville.
Brian Clifford Spall.
John William Stevens.
William Frederick Stones.
Donald Swaddle.
Robert Desmond Taylor.
John Theodore Terleski.
Alan Francis Thomas.
Gwen Jean Thomas.
Malcolm Thompson.
Anthony Noel Tizard.
Peter Torkington.
Cecil Nigel Turton.
William Perry Utermohlen, jun.
Hosang Pirojshaw Vandrewala.
Vladimir Vcelak.
David Pentland Veitch.
Peter Wade.
David Ronald de Mey Warren.
Kenneth Douglas Roland Washbourn.
Harry Wetherall.
Roy Arthur Webb.
Alec Webster.
Alfred Bentley Webster.
Norman Lord Wendler.
Bruce Oswald West.
Joseph Vicent Westwood.
Charles Edward Wheelock.
Frederick Allan Whittaker.
David James Whittingham.
Leslie Alfred Wiles.
John Alan Willey.
John Llewellyn Williams.
Arthur James Cochran Wilson.
John Charles Wiltshire.
Alfred Alexander Woolf.
James Bryan Lonsdale Worthington.

MEETING OF COUNCIL.

A Meeting of Council was held on February 16th, 1950.

The Report of the meeting of the Publication Committee held on January 19th, 1950, was adopted. This Report contained a recommendation that the practice of taking custody of manuscripts intended for publication only at a later date should cease.

The Report of the meeting of the Joint Library Committee held on January 25th, 1950, was received, and it was agreed to purchase a modern micro-film reader to replace the model already used in the Library.

The Report of the Chemical Council for 1948 was also received.

It was reported that the thanks of the Society had been conveyed to Dr. A. F. Campbell for a gift of the Society's publications.

Certain matters of a formal and financial nature were conducted.

RESEARCH FUND.

A meeting of the Research Fund Committee will be held in June next.

Applications for Grants, to be made on forms obtainable from the General Secretary, must be received on or before May 1st, 1950. Applications from Fellows will receive prior consideration.

Attention is drawn to the fact that the income arising from the Donation of the Worshipful Company of Goldsmiths is principally devoted to the encouragement of research

in Inorganic and Metallurgical Chemistry, and that the income from the Perkin Memorial Fund is to be applied to investigations relating to problems connected with the Coal Tar and Allied Industries.

MEETINGS OUTSIDE LONDON

AUSTRALIA.

" Some Properties of Soap Solutions," by Professor A. E. Alexander, M.A., Ph.D.

A joint meeting with Sydney University Chemical Society was held in the Lecture Theatre of the Chemistry Department of the University on February 8th, 1950, with Dr. S. J. Angyal in the Chair.

The Lecturer confined his attention mainly to the properties of the soaps as micelles. The oriented nature of the micelle formation, consisting both of ions and fatty acid, enabled substances like phenol to dissolve in the inner phase, and orient themselves in the same way. The percentage hydrolysis plotted against concentration shows a maximum and a minimum. At the critical concentration, which is half the concentration at the maximum point, the ratio of soap ion to free acid is unity. A formula was also derived from which the ratio of free acid in the micelle to that in the solution could be calculated. The alcohols (progressively more effective as the chain length increases) reduce hydrolysis by displacing the free acid in the micelle.

X-Ray-diffraction studies suggested that in very concentrated solutions, the micelles were built up in oriented lamellar form, but the most satisfactory interpretation proposes a structure of spherical micelles, held apart by forces of repulsion.

The Lecturer also dealt with viscosity and osmotic pressure of soap solutions and methods of arriving at the size of the micelle, which at the condition of minimum viscosity of solution, is approximately spherical.

At the conclusion, a vote of thanks to the Lecturer, proposed by Dr. T. Iredale, was carried with acclamation.

CAMBRIDGE.

" Reaction Mechanisms in Organic Chemistry," by Professor E. D. Hughes, F.R.S.

A joint meeting with the University Chemical Society was held in the Chemical Laboratory, Cambridge, on February 3rd, 1950, with Professor A. R. Todd in the Chair.

After a lively discussion, Dr. G. W. Kenner thanked the Lecturer on behalf of both Societies.

EDINBURGH.

" The Planning of Semi-technical Scale Experiments," by Dr. R. Holroyd.

A joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry was held in the North British Station Hotel on February 23rd, 1950, with Dr. I. A. Preece in the Chair.

Dr. Holroyd gave an authoritative and fascinating account of the difficulties encountered in converting semi-technical processes into full-scale production, and outlined by way of an epilogue some of the qualities and qualifications required by the research chemist in industry. A brisk discussion followed, and a vote of thanks, moved by Mr. F. J. Bolton, was carried with acclamation.

GLASGOW.

" Recent Advances in the Chemistry of the Steroids," by Professor F. S. Spring, D.Sc., F.R.I.C.

A meeting was held in the Royal Technical College on January 27th, 1950, with Professor J. W. Cook, in the Chair.

The Lecturer gave an extremely clear exposition of the history of steroid chemistry.

describing the immense advances made possible by the determination of the structure of cholesterol. The many types of steroid compounds found in nature were discussed, and the correlation of their structures were expounded in some detail. Finally, the chemistry of the much-discussed cortisone was dealt with; the many difficulties to be overcome in its commercial synthesis were explained, and the nature of some of the work now going on was described.

At the conclusion of the lecture a vote of thanks was moved by Professor P. D. Ritchie and carried with acclamation.

LEEDS.

"The Basis of Chemotherapeutic Research," by Dr. F. L. Rose, O.B.E., F.R.I.C.

A meeting was held in the Chemistry Department of the University on January 30th, 1950, with Professor F. Challenger in the Chair.

The Lecturer gave an account of the principles underlying the choice of substances likely to be of therapeutic value, and considered especially their rates of assimilation and elimination from the system. Examples were taken from compounds used against malaria and trypanosomiasis.

After an interesting discussion the thanks of the meeting were expressed by Professor R. E. Tunbridge.

"Some Recent Applications of Dipole-moment Measurements to Molecular Structure," by Professor H. D. Springall, M.A., D.Phil., F.R.I.C.

A joint meeting with the University Chemical Society was held in the Chemistry Department of the University on February 21st, 1950, with Dr. G. A. Jeffrey in the Chair.

Following a showing of Parts IV and V of the Gaumont-British Film "Atomic Physics," the Lecturer gave an account of the principles underlying the determination of dipole moments. He then discussed the application of the method to the investigation of the molecular structure of a number of compounds including pentaerythritol nitrate, the sydnones, and typical proteins.

After an interesting discussion the thanks of the meeting were expressed by Mrs. E. M. Carson.

LIVERPOOL.

"Some Aspects of Aromatic Substitution: the influence of Temperature and Catalysts," by Professor J. P. Wibaut, D.Sc.

A meeting was held in the Chemistry Lecture Theatre of the University on February 10th, 1950, with Professor A. Robertson in the Chair.

During his very stimulating lecture, Professor Wibaut dealt with the change from a nucleophilic reaction to a free-radical mechanism of substitution that occurs with halogens, and in particular with bromine, as the temperature rises, and with the concomitant remarkable change in the positions of substitution.

A vote of thanks, proposed by Professor T. P. Hilditch, was carried with acclamation.

SOUTHAMPTON.

"Modern Inorganic Stereochemistry," by Dr. R. S. Nyholm.

A joint meeting with the University College Chemical Society was held in the Physics Department of the University College on February 17th, 1950, with Dr. A. R. Burkin in the Chair.

Dr. Nyholm considered first the relationship between the steric properties of bond orbitals and the components involved in the hybridisation process, and discussed the application of magnetic-susceptibility measurements to the study of inorganic stereochemical problems. He then gave a detailed account of recent work on selected co-

ordination compounds of nickel, iron, and cobalt, and the determination of their probable structures.

After the discussion, a vote of thanks, proposed by Mr. J. Ramsay, was warmly accorded to Dr. Nyholm.

LIST OF APPLICATIONS FOR FELLOWSHIP

(Fellows wishing to lodge objections to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the Journal *for March*, 1950. *Such objections will be treated as confidential. The forms of application are available in the Library.)*

***Andrews, Patrick.** British. 114, Englishcombe Lane, Bath. Student at Bristol University. *Signed by :* J. K. N. Jones, F. H. Pollard, L. Hough.

***Baker, Brian,** B.Sc. (Birm.). British. Chemistry Department, The University, Edgbaston, Birmingham, 15. Research Student. *Signed by :* L. L. Bircumshaw, H. W. Melville, M. Stacey.

***Brady, Milton Neil,** B.Sc. (Sydney). British. 1, Joseph Street, Lidcombe, N.S.W., Australia. Research Student. *Signed by :* T. Iredale, L. E. Lyons, H. G. Holland.

***Cuws, Anthony Clifford,** B.Sc. (Lond.). British. 112, Rownhams Road, Maybush, Southampton. H.M. Forces. *Signed by :* I. G. M. Campbell, N. B. Chapman, R. E. Parker.

Chemerda, John Martin, M.S. and Ph.D. (Mich.). American. 890, Jacques Avenue, Rahway, New Jersey, U.S.A. Senior Research Chemist at Merck & Co., Inc., New Jersey. *Signed by :* E. M. Chamberlin, C. R. Addinall, M. Tishler.

Colledge, Raymond. British. 194, Stockton Road, West Hartlepool. Student. *Signed by :* A. H. Lamberton, J. Barrott, H. J. V. Tyrell.

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PAPERS RECEIVED

(List of papers received between February 10th and February 27th, 1950.)

"Syntheses in the octahydropyrrocoline series." By G. R. Clemo, N. Fletcher, G. R. Fulton, and R. Raper.

"Acylation reactions catalysed by strong acids. Part I. Evidence for the existence of the acetyl cation, $(CH_3{\cdot}CO)^+$, in solutions of concentrated aqueous perchloric acid in acetic anhydride." By H. Burton and P. F. G. Praill.

"The constitution of yohimbine and related alkaloids. Part IV. A synthesis of (+)-yohimbone." By G. A. SWAN.

"The constitution of yohimbine and related alkaloids. Part V. Some attempts to synthesise sempervirine." By G. A. SWAN.

"Anhydrides of polyhydric alcohols. Part XIV. Observations on the ring scission of 1 : 2-5 : 6-diepoxyhexane and 3 : 4-isopropylidene 1 : 2-5 : 6-dianhydromannitol." By L. F. WIGGINS and D. J. C. WOOD.

"The configuration of naturally occurring mixed glycerides. Part VI. The component fatty acids and glycerides of *Stillingia* tallows." By S. S. GUPTA and M. L. MEARA.

"Studies of trifluoroacetic acid. Part II. Preparation and properties of some trifluoroacetyl esters." By E. J. BOURNE, (MRS.) C. E. M. TATLOW, and J. C. TATLOW.

"Infra-red spectroscopic measurements of substituted pyrimidines. Part II. The absorption spectra of di-, tri-, and tetra-substituted pyrimidines." By I. A. BROWNLIE.

"The relative reactivity of aromatic double bonds. Part II. Addition of osmium tetroxide to substituted 1 : 2-benzanthracenes." By G. M. BADGER and K. R. LYNN.

"The relative reactivity of aromatic double bonds. PART III. The relation between double-bond character and the velocity of addition of osmium tetroxide." By G. M. BADGER.

"Studies in coal-tar bases. Part III. By-products of the hydrogenation of pyridine with Raney nickel." By J. IDRIS JONES.

"Studies in the synthesis of neurotropic and musculotropic stimulators and inhibitors. Part III. Derivatives of unsaturated ω-betaines." By F. BERGEL, A. COHEN, and N. C. HINDLEY.

"α-Methylenic reactivity in olefinic systems. Part IV. The structure of the dimeride formed by the stannic chloride catalysed polymerisation of trimethylethylene. Synthesis and characterisation of isomeric hexyl methyl ketones." By JOHN W. BAKER.

"*N*-Substituted amino-acids. Part I. A new method of preparation of dimethylamino-acids." By R. E. BOWMAN and (the late) H. H. STROUD.

"*N*-Substituted amino-acids. Part II. The reductive alkylation of amino-acids." By R. E. BOWMAN.

"*N*-Substituted amino-acids. Part III. The reductive alkylation of some di- and tripeptides. A new method of determining the 'end amino-acid' in polypeptides." By R. E. BOWMAN.

"The polarographic reduction of some heterocyclic molecules. Part II. Coumarin and certain derivatives." By A. J. HARLE and L. E. LYONS.

"The reaction of methyl radicals with olefins. Part IV. The reaction with tetrafluoroethylene and vinyl fluoride." By R. A. RAAL and C. J. DANBY.

"Synthetic analgesics. Part V. Compounds related to Pethidine." By A. L. MORRISON and H. RINDERKNECHT.

"Synthetic analgesics. Part VI. The synthesis of ketobemidone." By A. W. D. AVISON and A. L. MORRISON.

"Synthetic analgesics. Part VII. Metadine and related 3-phenylpiperidine derivatives." By A. W. D. AVISON and A. L. MORRISON.

"Synthetic analgesics. Part VIII. Further attempts to prepare 3-phenylpiperidine derivatives." By A. W. D. AVISON and A. L. MORRISON.

"Synthetic analgesics. Part IX. Synthesis of compounds related to Amidone." By A. L. MORRISON and H. RINDERKNECHT.

"Studies on fructosans. Part I. Inulin from dahlia tubers." By E. L. HIRST, D. I. MCGILVRAY, and E. G. V. PERCIVAL.

"The preparation of some 1-chloroalkane-1-carboxylic acids." By A. H. HORN, R. B. MILLER, and S. N. SLATER.

"Organic fluorides. Part III. Fluorination of aromatic hydrocarbons by using a gold catalyst." By R. N. HASZELDINE and F. SMITH.

"Organic fluorides. Part IV. Fluorination of hydroaromatic hydrocarbons by using a gold catalyst." By R. N HASZELDINE and F. SMITH.
"Compounds related to thiosemicarbazide. Part VI. Further routes to 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole and related compounds." By ERIC HOGGARTH.
"Compounds related to thiosemicarbazide. Part VII. Benzylthiosemicarbazides." By ERIC HOGGARTH and E. H. P. YOUNG.
"Some benziminazolyl-alanines." By P. Mamalis, V. Petrow, and B. STURGEON.
"A synthesis of 2-(2 : 3-dimethoxyphenyl)*cyclo*hexanone." By E. D. BERGMAN, R. PAPPO, and D. GINSBURG.
"Some experiments relating to œstrogenic indenes." By D. S. MORRIS.
"The separation of mixtures by continuous-extraction processes. Part II. The continuous stepwise extraction of a fixed quantity of a mixture of solutes." By J. D. A. JOHNSON.
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"The Fischer indole synthesis. Part IV. A kinetic investigation." By K. H. PAUSACKER and (the late) C. I. SCHUBERT.
"Contributions to the chemistry of synthetic antimalarials. Part IX. Some pyrimidine derivatives." By J. S. MOFFATT.
"Quinamine. Part V. *Epi*quinamine and *epi*cinchonamine." By C. C. J. CULVENOR, L. J. GOLDSWORTHY, K. S. KIRBY, and SIR ROBERT ROBINSON.

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III. *Pamphlets*

CALCAGNI, G. Il mio modello d'atomo. Frosinone 1949. pp. 36.

—— Il valore di certe teorie moderne. Frosinone 1949. pp. 109.

RESEARCH ASSOCIATION OF BRITISH RUBBER MANUFACTURERS. Thirty years of rubber research, 1919—49. Croydon 1949. pp. 27. ill.

SMITH, T. & H., LTD., Names that have made Edinburgh famous in the realms of chemistry. Edinburgh [n. d.]. pp. [32] ill.

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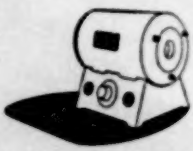

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SUMMARY. 9. Every paper must be prefaced by a short summary (50—250 words) setting forth briefly and in simple language the objects of the investigation and the results obtained. The summary should give any chemist a clear idea of what the investigation has achieved and should be independent of the main text. "Notes" do not require a summary.

STYLE. 10. Authors are requested to see that their papers conform, as nearly as possible, to the normal style, conventions, and conciseness of the *Journal*.

NOMENCLATURE. 11. Authors are expected to be familiar with the normal rules of nomenclature, but are invited to communicate with the Editor if in doubt or in special cases. Some of the principles followed in the *Journal* are reviewed in "Modern Chemical Nomenclature," by Dr. Clarence Smith (*J.*, 1936, 1067); reprints of this paper may be obtained by Fellows, price 2*d.* post free, from the General Secretary. Much valuable discussion will be found in "British Chemical Nomenclature," by Dr. A. D. Mitchell (Edward Arnold & Co., 1948). Authors should choose their symbols from the "Report of a Joint Committee of the Chemical Society, Faraday Society, and the Physical Society on Symbols for Thermodynamical and Physico-Chemical Quantities and Conventions Relating to their Use," copies of which may be obtained by Fellows, price 4*d.* post free, from the General Secretary.

NEW COMPOUNDS. 12. New compounds should be indicated by underlining the name at its first mention (excluding headings) in the Experimental section *only*, and by giving analytical results in the form: "Found: ———, ——— requires ———." Analytical results for compounds which have previously been adequately described in the literature should be given in the form: "Found: ———, Calc. for ———: ———."

ILLUSTRATIONS. 13. Illustrations accompanying the papers must be carefully drawn, preferably *twice* the size of the finished block (max. width 5 inches), *in Indian ink, on good white cartridge paper* (graph paper with faint blue lines is acceptable). Any illustration which seriously exceeds four times the size of the finished block will be returned to the author for re-drawing to a smaller scale. Lettering on the drawings, whether on the margin or in the body of the drawing, must not be in ink but must be inserted *clearly but lightly in pencil*. *Margins* of at least two inches must be left. Authors may, if they wish, submit in the first place clearly drawn pencil sketches instead of the completed diagrams, which, however, must be supplied before publication. Further information can be obtained from the Editor.

PROOFS. 14. Authors will be expected to pay the cost of any considerable changes made by them in proof, apart from the correction of printers' errors. See also paragraph 7.

PREPRINTS. 15. Each author, or joint author, receives 10 preprints (without covers) free of charge. A quotation for extra preprints and an order form will be sent with the proofs. The order form (and any necessary remittance) must be returned with the proofs.

This piece of accurate work was put forward in Scott's thesis for D.Sc. of Edinburgh University (1883).

Composition of Water by Volume.—Time was found for his researches while in the North, and the paper (1888) on the composition of water by volume comes from his laboratory in Durham School. In a later paper on the same subject from Cambridge, he refers to this as a preliminary note on a subject on which no work has been done since the time of Gay-Lussac and Humboldt.

In Professor Partington's book on " The Composition of Water " (London, G. Bell & Sons, 1928) will be found a historical account of the earlier work on this subject by Cavendish, Lavoisier, Monge, Priestley, Gay-Lussac, and Humboldt and details are given of the experimental methods of Dumas, Morley, Scott, and Burt and Edgar. Partington quotes from Scott's paper (1894) : " Throughout I have endeavoured to use the simplest apparatus possible and to prepare the gases themselves from only the purest materials, and those of the simplest composition that I could find, so that no purification should be required and all unnecessary contact with other chemical substances avoided, to work with an apparatus of glass throughout, so that no diffusion could take place, and finally, so to work, that with a given amount of materials, I might compare the gas given off in the first fractions continuously to the last fractions, and thus endeavour to detect any possible impurity, either by variation of the ratio, or by actual observation from the residual gas."

Then follow descriptions of the sources of the hydrogen and of the oxygen, and a sketch of Scott's apparatus is reproduced. Partington remarks on the high degree of precision, very pure gases being used, the gases measured with great accuracy, their temperature and pressure being carefully controlled throughout the experiment, and the analysis of the residual gas being exact.

Examples of typical experiments are given in the paper, and the ratio of oxygen to hydrogen by volume is found to be 1 : 2·0045 at temperatures of 14° to 18°, both gases being measured at the same temperature. If, however, the values for the coefficient of expansion of oxygen and hydrogen are taken into account the value of 2·00285 at 0° is found for the ratio of the combining volumes. This value, combined with the value 15·882 for the ratio of densities found by Lord Rayleigh, gives the atomic weight of oxygen 15·862, and, if oxygen is taken as 16, of hydrogen 1·008, the present accepted figure being 1·0078.

In a very accurate series of experiments in 1915 Burt and Edgar made use of facilities not available to Scott, and measured the gases actually at 0° and 1 atm., thus avoiding the correction for expansion. They obtained for the above ratio 1 : 2·00288.

Atomic Weight of Carbon.—In a review of the various determinations of the atomic weight of carbon (1897), Scott called attention to discrepancies among these and indicated possible sources of error. Already Dewar and Scott (1883) had employed another method—that of titrating with silver the bromine in the hydrobromide of triethylamine, but the results were disappointing on account of the difficulty of getting pure triethylamine together with a slight tendency of its hydrobromide to hydrolyse.

Scott returns to the subject (1909) when he uses the elegant method of titrating tetra-alkylammonium bromides, choosing these because of their relatively stable character and easy purification. This paper gives the details of his experiments on titrating tetra-alkylammonium bromide with silver and, with the same silver, ammonium bromide. By subtraction the equivalent of a hydrocarbon C_5H_{14} is derived. Thus with silver at 107·88, the atomic weight of carbon is found to be 12·017 from tetramethylammonium bromide, the present accepted figure being 12·010, silver being 107·880.

By another method in which carbon monoxide and oxygen were exploded in the apparatus used for determining the composition of water by volume (1894) a value of 11·99 was deduced for carbon (1904).

From a few experiments (1909) on the combustion of naphthalene and of cinnamic acid, the value of the atomic weight of carbon comes out at C = 12·00. " The cause of the discrepancy between these results and those derived from the alkylammonium bromides remains still to be discovered."

Atomic Weight of Nitrogen.—By the titration of ammonium chloride and bromide against silver Scott obtained results lower than those of Stas, and this has been confirmed especially by Lord Rayleigh and by Whytlaw-Gray who, using nitric oxide (*J.*, 1905, **87**, 1601), obtained 14·01, practically the same value as Scott. The most recent International Tables give N = 14·008.

Atomic Weight of Tellurium.—This is described as a preliminary notice (1902) and has the object of confirming the value for the atomic weight of tellurium, which has an anomalous

position in the Periodic Table in being higher than that of iodine. Scott's method was to make careful determinations of the halogens in the stable salts trimethyltellurium bromide and iodide. Taking the values O = 16, C = 12·00, H = 1·0075, I = 126·85 and Br = 79·95 tellurium was found to have an atomic weight of 127·7, the value given in the recent tables being 127·61. Tellurium with its abundance and range of isotopes thus occupies an anomalous position in the Periodic Table with regard to iodine which has none.

Other Papers.—These are either of general interest such as a new series of mixed sulphates of the vitriol group (1897), a new sulphide of arsenic (1900), the vapour density of hydrazine hydrate (1904), correction of weighings in air to vacuum (1909); or are descriptions of methods for preparing substances used in determination of atomic weight, such as preparation of pure hydrobromic acid (1900), of alkyl derivatives of sulphur, selenium, and tellurium (1904), and of pure bromine (1913).

Services to Art and Archæology. (By Dr. H. J. Plenderleith.)—Scott's contribution to the problems of art and archæology was characteristically that of the experimenter and teacher rather than the writer of textbooks, and his aim was to discover and publish simple methods of treatment that would be safe in the hands of those not having the advantage of a technical or scientific background.

A great source of inspiration was his visit to Luxor for the winter season (1923—1924) at the invitation Howard Carter to act as consulting chemist in devising methods of preserving the objects from Tut-Ankh-Amun's tomb. It was this intimate study of antiquity in the field in all its frail beauty and the confidence that science had so much to contribute that provided him with the incentive to create a permanent scientific service in the the British Museum.

If primarily concerned with the problems of metallic corrosion or saline incrustations in exhumed material, work at the British Museum soon developed important off-shoots scarcely to be anticipated in the early days. For example, a body of knowledge was gradually acquired which could be applied to differentiate the genuine antiquity from the false or to classify types of ethnic culture and solve problems of age and provenance. The value of such work could be assessed in terms understood and appreciated by H.M. Treasury. Once established on a permanent basis it was possible to afford unstinting help to other institutions, museums, libraries and picture galleries.

It was not to be expected that intricate operations would be undertaken by a man of his years; what was of lasting value was the standing that science was given in museum and gallery circles by his great knowledge, his strong personality and his genius for friendship in all walks of life. His advice was sought from every quarter of the civilised world and freely and promptly given wherever it would be of value in the interests of art, archæology or science.

This was his contribution: to represent science as the servant of the arts, to disarm suspicion where it existed, to demonstrate what might by this fruitful liaison be achieved and thus to lay the foundation for a partnership between art and science of mutual benefit for all time.

Alexander Scott died at Ringwood, Hampshire, on 10 March 1947. In 1906 he married Agnes Mary, daughter of Dr. W. J. Russell, F.R.S., and leaves no family.

In the preparation of this Notice, I have been indebted to Dr. Scott's widow and his family for biographical material, and very notably to Dr. H. J. Plenderleith, Scott's successor as Director of the British Museum Laboratory, for his contribution on the period 1919 to 1938, and for his appreciation of Scott's "Services to Art and Archæology."

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152. *The Effect of Varying the Cation in Some Organic Reactions requiring an Alkaline Medium.*

By O. L. Brady and J. Jakobovits.

In the methylation of lactam–lactim tautomerides in alkaline media with methyl sulphate the nature on the alkali appreciably alters the ratio of *O*- to *N*-methylation, the most marked difference being between sodium hydroxide and a tetra-alkylammonium hydroxide.

In the Reimer–Tiemann reaction, with sodium hydroxide the ratio of *ortho*- to *para*-substitution is approximately 2 : 1, with cæsium hydroxide 1 : 1, and with methyltriethylammonium hydroxide 1 : 2.

Kinetic studies have been made of the hydrolysis of a number of esters. With methyl sulphate, in 0·1*N*-alkali in aqueous methyl alcohol, change of alkali has little effect; but with ethyl sulphate in 1*N*-alkali in aqueous methyl alcohol, passing from sodium hydroxide to methyltriethylammonium hydroxide approximately doubles the rate constant.

The hydrolyses of alkali alkyl phthalates $C_6H_4(CO_2M)CO_2R$, where M is Na or $NMeEt_3$, with the corresponding alkali hydroxide MOH show no difference in rate constants in aqueous solution, but in aqueous methyl alcohol the hydrolysis when M = Na has a rate constant about ten times that found when M = $NMeEt_3$.

An explanation of these results is suggested depending on formation of co-ordination complexes.

It has long been known that use of sodium and silver salts often gives different products in the alkylation of compounds capable of tautomerism, *e.g.*, in the methylation of isatin, cyanides, and nitrites, but the fact that these reactions are often, of necessity, carried out in hetereogenous media, with the solid salt, has deterred speculation on the causes of the different directions in which they proceed. A classical example of the effect of a change of metal within the same

group of the Periodic Table is the Kolbe–Schmidt reaction, in which sodium phenoxide heated under pressure with carbon dioxide gives sodium salicylate but potassium phenoxide under similar conditions gives a large proportion of potassium *p*-hydroxybenzoate (Kolbe, *J. pr. Chem.*, 1874, [ii], **10**, 95; Brunner, *Annalen*, 1907, **351**, 326; Tijmstra Bz, *Ber.*, 1905, **38**, 1375; Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 3029). Neogi (*J.*, 1906, **89**, 1900; 1914, **105**, 2371; 1916, **109**, 701) found that when a sodium alkyl sulphate was fused with sodium nitrite the ratio of the yields of alkyl nitrite and nitroparaffin was 0·36 : 1, whereas it was 1·9 : 1 when the potassium salts were used. Here again solid salts were employed.

Graebe (*Annalen*, 1905, **340**, 244) noted that dry potassium benzoate gave, with methyl sulphate, a better yield of methyl benzoate than was obtained from sodium benzoate, and that potassium benzoate was methylated by potassium methyl sulphate more readily than by sodium methyl sulphate. Ullmann (*Ber.*, 1900, **33**, 2774; *Annalen*, 1902, **327**, 104) found that phenols were methylated equally well in sodium hydroxide or potassium hydroxide solution or in the form of the solid sodium or potassium phenoxide. Klemenc (*Monatsh.*, 1917, **38**, 553) found that, in the methylation with methyl sulphate of quinol and resorcinol in aqueous alkali, potassium hydroxide gave a much smaller yield than sodium hydroxide, suggested that the former hydrolysed methyl sulphate faster than did the latter, and confirmed this by measuring the rate constants of the heterogeneous hydrolysis of methyl sulphate by N-alkali at 11°, finding $k_{KOH}/k_{NaOH} = 1{\cdot}25$.

These reactions were carried out in a heterogeneous medium and might be accounted for by different rates of diffusion of methyl sulphate into the alkaline solutions, or by greater solubility of methyl sulphate in potassium hydroxide solution, as well as by a specific effect of the cation.

Walden and Centnerszwer (*Z. Elektrochem.*, 1909, **15**, 310) however, measured the rate constants of the reaction

$$Me_2SO_4 + MCNS = MeCNS + MeMSO_4$$

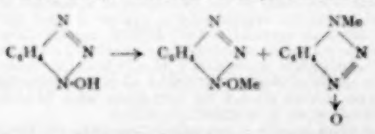
where M = Na or K, in homogeneous methyl alcoholic solution and found for 0·5N-solution $k_K/k_{Na} = 1{\cdot}14$, for 0·25N-solution 1·06, and for 0·125N-solution 1·34.

Other reactions are recorded in which the rate constants with different alkalis appear to be unchanged; for example, Meyer (*Z. anorg. Chem.*, 1921, **115**, 212) could not detect an appreciable difference in the rate constants for the hydrolysis of ethyl acetate by the hydroxides of lithium, sodium, potassium, rubidium, and cæsium in approximately N./10-solution. It will be shown later, however, that this is too low a concentration to show an effect of variation in the cation.

Reimer and Tiemann (*Ber.*, 1876, **9**, 824) state that, contrary to experience in the Kolbe–Schmidt reaction, in their synthesis of hydroxy-aldehydes the proportion of *ortho*- and *para*-derivatives is unaffected by changing from sodium hydroxide to potassium hydroxide; and Walden (*Ber.*, 1899, **32**, 1833), for the hydrolysis of α-chlorosuccinic acid by 0·4N-alkali, found that the rotation of the malic acid obtained differed considerably according to the alkali used (LiOH +100°; NaOH +150°; KOH +425°; RbOH +440°; aq. NH_3 +460°).

The effect of varying the cation has now been investigated further, first, on the products of methylation of tautomeric compounds, secondly on the proportion of *ortho*- : *para*-substitution in the Reimer–Tiemann reaction, and thirdly on the hydrolysis of esters.

In studying methylation it was necessary to choose a compound, stable to alkali, which gave reasonable amounts of the isomeric methyl derivatives. Such was found in 1-hydroxybenztriazole which with methyl sulphate in 2N-alkli gave two methyl derivatives (Brady and Reynolds, *J.*, 1928, 198; 1931, 1273). The ratio *O*-Me/*N*-Me formed in 2N-MOH was LiOH



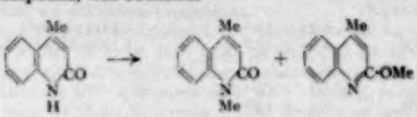
1·12, NaOH 0·97, KOH 1·02, RbOH 1·17, CsOH 1·26, and $NMeEt_3$·OH 1·53. Although the accuracy of the results is not sufficient to dogmatise on the effect of the change from one alkali-metal to another the difference between sodium hydroxide and methyltriethylammonium hydroxide seems well outside the limit of experimental error, and probably the difference between sodium hydroxide and cæsium hydroxide is also significant.

Since sodium hydroxide and methyltriethylammonium hydroxide gave the greatest

difference, in subsequent experiments the hydroxides of cæsium and rubidium were not always used on account of the lengthy task of continually recovering the limited amounts of the materials.

Lithium hydroxide could not always be employed owing to the sparing solubility of lithium salts, which crystallised out and altered the conditions of the experiment.

2-Hydroxylepidine can be methylated by methyl iodide in methyl alcohol in the presence of alkali methoxide. With sodium methoxide, the ratio *N*-Me/*O*-Me is 4·5, with potassium methoxide is 10·8, and with $NMeEt_3$·OMe is ∞. In the last case no trace of the *O*-Me compound, but 82% of the *N*-Me compound, was obtained.



The improvement in technique afforded by the determination of aldehydes by dinitrophenylhydrazine has enabled us to show the effect of change of alkali in the Reimer–Tiemann reaction where the original authors failed (*loc. cit.*). In 15N-alkali the *ortho-para*-ratio was NaOH 2·08, KOH 1·24, CsOH 0·98, and $NMeEt_3$·OH 0·52. In 2N-alkali the difference almost disappeared, the ratio being NaOH 0·90, KOH 0·91, and $NMeEt_3$·OH 0·86. In 15N-lithium hydroxide the ratio was 0·9 but, as much lithium phenoxide crystallised out, the concentration in solution was low.

The yields of aldehyde in the Reimer–Tiemann reaction were of the usual low order (Armstrong and Richardson, *J.*, 1933, 496) and the results would not be credible were they not so remarkable and repeatable within reasonable limits. On changing from sodium hydroxide to methyltrimethylammonium hydroxide the product changes from *o*-/*p*- = 2 : 1 to *o*-/*p*- 1 : 2.

The experiments so far described did not admit of very accurate measurements, so a kinetic investigation has been made of the hydrolysis of esters by various alkalis in homogeneous media, with the following results:

Hydrolysis of Me_2SO_4 *in 50% v/v aqueous* MeOH *at 0°.*

Alkali.	Concn., N.	10^3k_1, sec.$^{-1}$.
NaOH	0·1000	2·61
KOH	0·1022	2·57
$NMeEt_3$·OH	0·1037	2·52

The differences are within the experimental error, so at this concentration of alkali no effect is observed.

Methyl sulphate in aqueous methyl alcohol is decomposed much too rapidly by stronger alkalis for kinetic measurements to be made, so the less reactive ethyl sulphate was substituted, with results as follows:

Hydrolysis of Et_2SO_4 *in 90% v/v aqueous* MeOH *at 0°.*

Alkali.	Concn., N.	10^3k_1, sec.$^{-1}$.
NaOH	1·0328	7·5
KOH	1·0328	9·5
$NMeEt_3$·OH	1·0534	16·9

Owing to the difficulty in obtaining accurate results in kinetic measurements at these concentrations, it would be unwise to place too much reliance on the difference between sodium and potassium hydroxides, but the difference between sodium and methyltriethylammonium hydroxides is too large to be due to experimental error.

The use of methyl alcohol as a solvent introduces possible complications, so esters were investigated which could be hydrolysed in homogeneous aqueous solution.

The hydrolysis of methyl methanesulphonate in 1·026N-aqueous sodium hydroxide at 25° gave $k_2^{25} = 5·5 \times 10^{-4}$ sec.$^{-1}$ and in 1·026N-aqueous methyltriethylammonium hydroxide gave $k_2^{25} = 9·4 \times 10^{-4}$ sec.$^{-1}$.

The alkali alkyl phthalates *o*-$RO_2C·C_6H_4·CO_2M$ (R = alkyl, M = Na, K, or $NMeEt_3$) at 25° or 0°, in both water and 90% methyl alcohol, were hydrolysed with the corresponding alkali hydroxide; for comparison ethyl acetate was hydrolysed in 90% methyl alcohol at 0°. The rate constants are given in Table I. In 0·1N-alkali no effect is observable, even in aqueous methyl alcohol. In N-alkali the effects are not marked in aqueous solutions, except in the case

TABLE I.

Water.		90% Methyl alcohol.	
Alkali (+)-sec.-octyl phthalate at 25°.			
1·026*n*-NaOH	$6·2 \times 10^{-4}$	—	—
1·026*n*-$NMeEt_3$·OH	$6·95 \times 10^{-4}$	—	—
Alkali sec.-butyl phthalate at 25°.			
1·026*n*-NaOH	$1·8 \times 10^{-4}$	1·047*n*-NaOH	$1·4 \times 10^{-5}$
		0·985*n*-KOH	$1·1 \times 10^{-5}$
1·026*n*-$NMeEt_3$·OH	$1·8 \times 10^{-4}$	1·077*n*-$NMeEt_3$·OH	$0·092 \times 10^{-5}$
Alkali methyl phthalate at 25°.			
1·005*n*-NaOH	$4·33 \times 10^{-4}$	0·9847*n*-NaOH	$1·25 \times 10^{-4}$
1·026*n*-$NMeEt_3$·OH	$3·5 \times 10^{-4}$	1·108*n*-$NMeEt_3$·OH	$0·14 \times 10^{-4}$
Alkali methyl phthalate at 0°.			
1·005*n*-NaOH	$5·0 \times 10^{-4}$	—	—
1·026*n*-$NMeEt_3$·OH	$5·0 \times 10^{-4}$	—	—
Ethyl acetate at 0°.			
—	—	1·0328*n*-NaOH	$1·66 \times 10^{-4}$
—	—	1·0328*n*-KOH	$1·66 \times 10^{-4}$
—	—	1·0328*n*-$NMeEt_3$·OH	$1·17 \times 10^{-4}$

of methyl methanesulphonate where $k^{25}_{Am}/k^{25}_{NaOH} = 1·7$ (k_{Am} refers to the quaternary ammonium base), but in 90% methyl alcohol in the hydrolysis of ethyl sulphate $k_{Am}/k_{NaOH} = 2·2$, of alkali *sec.*-butyl phthalate $k^{25}_{Am}/k^{25}_{NaOH} = 0·066$ and of alkali methyl phthalate $k^{25}_{Am}/k^{25}_{NaOH} = 0·112$.

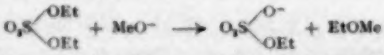
The most significant fact is that in the same solvent methyltriethylammonium hydroxide hydrolyses ethyl sulphate more rapidly, but an alkali alkyl phthalate less rapidly, than does sodium hydroxide. It seems impossible to suppose that the difference in rate constants is due simply to variation of hydroxyl-ion concentrations in the solutions, and one must seek an explanation in the nature of the compound hydrolysed.

The first difference in nature of the substance hydrolysed is that whereas the esters of carboxylic acids on alkaline hydrolysis normally undergo acyl–oxygen fission (see Day and Ingold, *Trans. Faraday Soc.*, **1941**, **37**, 689, for a summary of the evidence) methyl methanesulphonate on aqueous alkaline hydrolysis undergoes alkyl–oxygen fission by a bimolecular mechanism (Ader, University of London Ph.D. Thesis, "Mechanism of Sulphonic Ester Hydrolysis," **1949**), and ethyl sulphate on interaction with alcohol in the presence of water and sodium hydroxide undergoes mainly an alkyl–oxygen fission (Lauder and Green, *Nature*, **1946**, **157**, 767).

In aqueous methyl alcoholic solutions both hydroxyl and methoxyl ions will exist: $MOH \rightleftharpoons M^+ + HO^-$; $HO^- + HOMe \rightleftharpoons H_2O + MeO^-$. In acyl–oxygen fission attack by MeO^- does not lead to a change in the acid titre:

$$R'\cdot CO_2R + MeO^- \rightleftharpoons R'\cdot CO_2Me + RO^-$$

but with alkyl–oxygen fission the titre changes:



An explanation might be suggested, therefore, that in a solution of methyltriethylammonium hydroxide in 90% methyl alcohol the methoxyl-ion concentration is higher than in a corresponding solution of sodium hydroxide, and vice versa for the hydroxyl-ion concentration. This would account for the slower action of the ammonium base on the carboxylic esters and might account for its more rapid action on ethyl sulphate. If this were the explanation one would expect a similar change of the same order in the rate constant of the hydrolysis of ethyl acetate, but in this case a decrease of only 30% is observed whereas in the phthalates there is a factor of ten.

In experiments using methyl alcohol as a solvent a complication may arise when a different alcohol is produced from the ester, since the rate constant may be a composite figure representing the following reactions:

$$R'\cdot CO_2R + HO^- \longrightarrow R'\cdot CO_2H + RO^-$$
$$R'\cdot CO_2R + MeO^- \rightleftharpoons R'\cdot CO_2Me + RO^-$$
$$R'\cdot CO_2Me + HO^- \longrightarrow R'\cdot CO_2H + MeO^-$$

This might be the case for the hydrolysis of alkali *sec.*-butyl phthalate in methyl alcohol, but not for the hydrolysis of alkali methyl phthalate in methyl alcohol. Since, however, the

rate constant for the hydrolysis of sodium *sec.*-butyl phthalate by sodium hydroxide is approximately one-tenth of that of sodium methyl phthalate by sodium hydroxide and the rate constant for the hydrolysis of methyltriethylammonium *sec.*-butyl phthalate by methyltriethylammonium hydroxide is also approximately one-tenth of that of methyltriethylammonium methyl phthalate, it can be assumed that this complication plays but a small part in the difference between the rate constants obtained with sodium hydroxide and methyltriethylammonium hydroxide. It seemed desirable, in the first instance, to confine these experiments to one solvent alcohol, to avoid ambiguities caused by possible variation in the alkoxyl : hydroxyl ratio in changing from one alcohol to another, or by different facilities of various alcohols for forming co-ordination compounds.

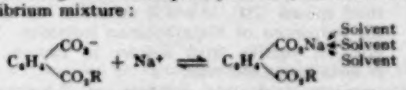
It might be held that different solvation of the cations would have an influence. The primary solvation would be in the order $Na^+ > K^+ \gg MeEt_3N^+$ (cf. Bockris, *Quart. Reviews*, 1949, **3**, 173), and if water molecules solvated the cations more readily than methyl alcohol molecules the concentration of HO^- compared with MeO^- in 90% methyl alcohol would be reduced more by Na^+ than by $MeEt_3N^+$ owing to the removal of water in the equilibrium $HO^- + HOMe \rightleftharpoons MeO^- + H_2O$, but this would decrease the rate of hydrolysis by sodium hydroxide compared with that by methyltriethylammonium hydroxide. If, on the other hand, there was preferential solvation by methyl alcohol, a greater increase in HO^- concentration would result from Na^+ than from $MeEt_3N^+$, but owing to the high proportion of methyl alcohol the difference would probably be very small. Further, solvation would not surmount the difficulty of explaining an opposite effect of the cations in the hydrolysis of ethyl sulphate and methyl methanesulphonate.

Neither of these explanations can be used to account for the differences observed in the alkylation of tautomerides and in the Reimer–Tiemann reaction in which alteration in the orientation of substitution is observed.

An explanation, which covers all cases and can be extended to numerous other reactions where a difference is observed between the alkali hydroxides, concerns the ease with which the different cations can form stable covalent links with the organic compound under investigation.

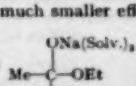
Other evidence leads to the conclusion that, with the alkali metals, the tendency to form stable covalent bonds decreases from sodium to cæsium; the nitrogen in the tetra-alkylammonium ion, having already a completed octet of electrons, is unlikely to form other stable covalent bonds.

In the case of the half esters of phthalic acid a solution of the tetra-alkylammonium salt may, therefore, be regarded as being almost completely ionised, but a solution of the sodium salt will consist of the equilibrium mixture :

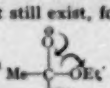


The compound undergoing hydroysis in the two cases will therefore not be the same. In view of the negative charge on the carboxyl group in the ion this will hydrolyse less rapidly than the sodium co-ordination compound. The equilibrium in the sodium salt would move to the right on passing from an aqueous to an alcoholic medium and to the left on reduction of concentration of the reactants in the solvent. The experimental rate constants are in accordance with these considerations.

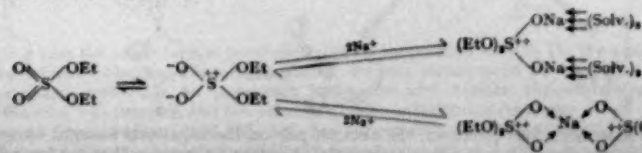
In ethyl acetate a much smaller effect would be expected although it might still exist, for in the transition state



would be less likely to give the acid than

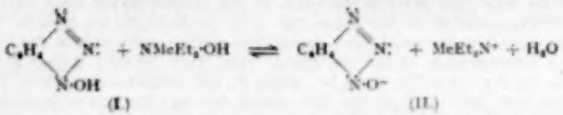


In ethyl sulphate the sodium ions can accept electrons from the co-ordinately linked oxygens and from the solvent, thus :



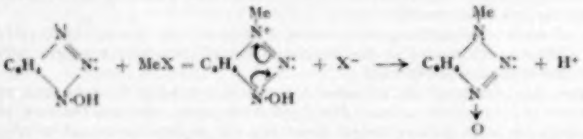
Any such tendency to neutralise the negative charge on oxygen will enhance the positive charge on sulphur which would favour alkyl–oxygen fission, but in view of the tendency of the sulphur atom to increase its octet the hydroxyl ion will be strongly attracted to the S^{++} centre. If only one hydroxyl ion attacks, the sulphur atom will still bear a positive charge and there will be little tendency for acyl–oxygen fission to occur with escape of EtO^-; this might be expected only if two hydroxyl ions attacked at the same time, but such a termolecular reaction would be very slow. The sodium complex is accordingly less easily attacked by sodium hydroxide than by the tetra-alkylammonium hydroxide.

We turn now to the methylation of tautomeric compounds; in solutions of 1-hydroxybenztriazole in tetra-alkylammonium hydroxide the undissociated compound (I) and the ion



(I) (II)

(II) will be present. In (I) attack will occur at the oxygen atom, leading to the formation of 1-methoxylbenztriazole, but in (I) attack at nitrogen will be favoured, followed by elimination of a proton owing to electron withdrawal by the N^+, leading to the formation of 3-methylbenztriazole 1-oxide.



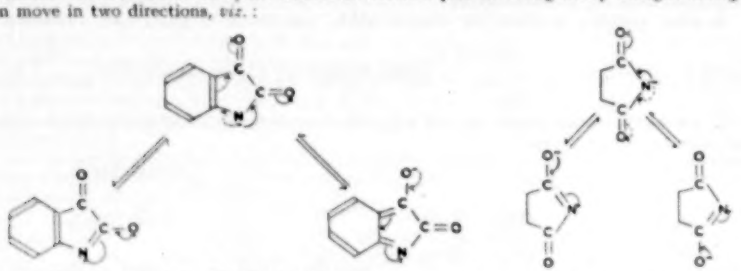
Brady and Reynolds (*loc. cit.*) showed that in the absence of alkali and solvent 1-hydroxybenztriazole suffered only *N*-methylation, and Brady and Day (*J.*, **1923**, **123**, 2258) showed that in the substituted hydroxybenztriazoles (*e.g.*, the nitro-compounds) the more acidic the compound, and consequently the less hydrolysed its salts in aqueous solution, the greater the preponderance of *O*-alkylation.

(III)

In the presence of sodium hydroxide the solution will contain a third species (III), in which attack at nitrogen will be favoured; so the proportion of *N*-methylation increases. The proportion of (III) falls on passing from sodium to cæsium, so the proportion of *N*-methylation also falls.

A methyltriethylammonium hydroxide solution of 2-hydroxylepidine, which, on our argument, should contain essentially ions only, gave, on methylation, only the *N*-methyl compound.

No explanation seems to have been advanced for the *N*- rather than the *O*-alkylation of the sodium salts of lactam–lactim tautomerides such as isatin, phthalimide, and 2-hydroxypyridine. In isatin and the cyclic imides an electron pair on a negatively charged nitrogen can move in two directions, *viz.*:

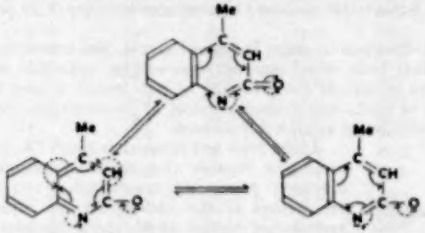


but, in the mesomeric ions produced, the electron pair on the negatively charged oxygen can move only in one direction. It seems reasonable, therefore, to suppose that the ion with the

negative charge associated with nitrogen contributes more than do the ions with the negative charges associated with oxygen to the structure of the resonance ion and, consequently, that the nitrogen atom will be attacked by an electrophilic reagent such as Me^+. A similar explanation can be offered for the exclusive *C*-alkylation of, *e.g.*, ethyl sodiomalonate.

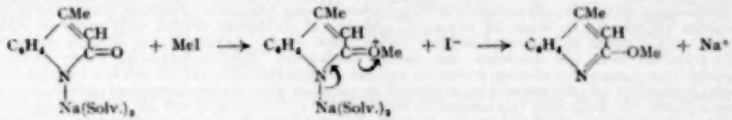
$$\delta\ominus C(OEt)\!=\!CH\!-\!C(OEt)\!=\!O\ \delta$$

The case of 2-hydroxylepidine or 2-hydroxypyridine is more complex. When the negative charge is on nitrogen the electron pair can again move in two directions, whilst in the ions with the charge associated with oxygen the electron pair can move only in one direction, but the latter ions are interconvertable by electron shift within the benzenoid ring, thus:



It is noteworthy that the ion of hydroxybenztriazole, which becomes alkylated on oxygen, does not exhibit this peculiarity, nor does the oximino-ion $R{\cdot}CH{=}N{-}O^-$, which also becomes alkylated on oxygen (Brady and Goldstein, *J.*, **1926**, 2403; Brady and Jackson, unpublished).

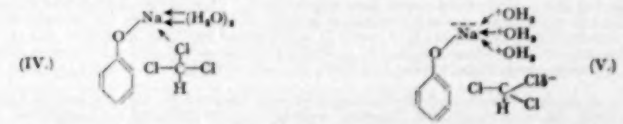
As the negative charge on the 2-hydroxylepidine ion is associated mainly with the nitrogen atom, *N*-alkylation is explicable in tetra-alkylammonium hydroxide solution, but in sodium hydroxide solution, owing to the tendency to form a co-ordination compound, some *O*-methylation can occur by the following mechanism:



In the Reimer–Tiemann reaction the significant stage is entry of the $-CHCl_2$ into the nucleus

$$C_6H_5{\cdot}OM + CHCl_3 + M^+ + HO^- = MO{\cdot}C_6H_4{\cdot}CHCl_2 + M^+ + Cl^- + H_2O$$

In the presence of 15N-tetra-alkylammonium hydroxide no un-ionised phenol would be present and no co-ordination compound, so that the only reacting species would be the phenoxide ion. In these circumstances substitution yields approximately 2 parts of *p*- to 1 of *o*-compound; the preponderance of *para*-substitution is in accordance with expectation in view of the strong electromeric effect of the negative pole. When 15N-sodium hydroxide is employed a different state of affairs can exist: either chloroform or solvent molecules or both can co-ordinate with the sodium:



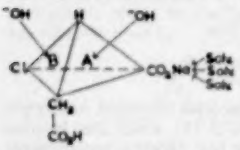
In either case the chloroform is presented to the *ortho*-position since in (V) the positive charges on the solvent molecules will tend to attract the lone electrons on the chlorine. On passing from sodium hydroxide to potassium hydroxide and cæsium hydroxide the extent of co-ordination will decrease and the amount of *ortho*-substitution decreases.

Ingold (*Ann. Reports*, **1926**, **23**, 142) has suggested a similar explanation of the nuclear alkylation of phenols through their salts in non-ionising solvents where the substituent enters

exclusively at the *ortho*-position. The same idea has been invoked in the Kolbe–Schmidt reaction which has been shown to involve, probably, direct substitution at nuclear carbon and not intermediate formation of sodium phenyl carbonate (Tijmstra Bz, *Ber.*, 1905, **38**, 1375; Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 3029).

The above authors state no reasons for the difference in behaviour between sodium and potassium phenoxide, but it could be caused by a reduced stability of the potassium co-ordination compound.

When the Reimer–Tiemann reaction is carried out in less concentrated solutions, *e.g.*, in 2N-alkali, the *ortho–para* ratio, when tetra-alkylammonium hydroxide is used, corresponds to the substitution of the phenoxide ion plus that of free phenol formed by hydrolysis. When 2N-sodium hydroxide is used, only a small amount of co-ordination compound is formed, so that the *ortho–para* ratio is not appreciably altered.



If the view put forward is correct a number of other phenomena are capable of a similar explanation. In the Walden inversion previously mentioned, if co-ordination compounds are formed at the carboxyl group attached directly to the asymmetric carbon atom, steric hindrance might well hinder the approach of the hydroxyl ion to face *A* as required for inversion, and approach to face *B* involving no inversion would be favoured. The increase in inversion found by Walden (*loc. cit.*) was in the order LiOH < NaOH < KOH < RbOH < NH_4OH, that is, as the probability of co-ordination compound formation decreased.

Experimental.

Preparation of Alkalis.—Solutions of sodium hydroxide and potassium hydroxide were made up with the usual precautions to avoid all but small amounts of carbonate, diluted with water or methyl alcohol, and checked against standardised hydrochloric acid. Rubidium and cæsium hydroxides were prepared from the sulphates and barium hydroxide. Methyltriethylammonium hydroxide solutions were prepared by shaking a weighed amount of the iodide with the solvent and 1·3 equivalents of silver oxide for 10—20 hours until a filtered test portion gave no precipitate with nitric acid and silver nitrate; the precipitate was allowed to settle, and the solution siphoned off, titrated with hydrochloric acid, and the strength adjusted. Precautions were taken to avoid contamination with carbon dioxide.

Methylation of 1-Hydroxybenztriazole.—The hydroxybenztriazole was prepared *via o*-nitrophenylhydrazine. 1-Methoxybenztriazole and 3-methylbenztriazole 1-oxide were prepared for test of the analytical method (Brady and Reynolds, *J.*, 1928, 196).

The hydroxybenztriazole (1·5 g.; 0·011 mol.) was dissolved in 2N-aqueous alkali (6 c.c.), and redistilled methyl sulphate (1·1 c.c.; 0·011 mol.) added. The mixture was thoroughly shaken for 10 minutes whereupon the solid ethers began to separate, and after 50 minutes were repeatedly extracted with chloroform. The combined extracts were dried (Na_2SO_4), the solvent was removed, and the residue dried in an evacuated desiccator. The relative amounts of *O*- and *N*-methyl derivatives were determined by Zeisel and Herzig–Meyer estimations. As the amounts of silver iodide formed did not correspond to the total quantity of the mixed *N*- and *O*-methyl compound employed, determinations were carried out with the pure derivatives. The *O*-methyl compound gave an almost theoretical yield of silver iodide, but the *N*-methyl compound gave approx. 61%. This determination was reproducible within 1%; the loss is probably caused by migration of some of the methyl into the benzene nucleus on heating of the hydriodide. In column 6 of Table II a correction has been applied to the content of *N*-methyl compound which is calculated from (1 + 39/61) time the actual weight of silver iodide. The total amount of methyl compounds (column 7 of Table II) then varies from 87 to 100%, with an average of 93%.

Methylation of Hydroxylepidine.—2-Hydroxylepidine was prepared by the method of Laver and Kaskow (*Org. Synth.*, **24**, 68); the *O*- and *N*-methyl derivatives were prepared for comparison (Knorr, *Annalen*, 1886, **236**, 97; Knorr and Autrick, *Ber.*, 1884, **17**, 2876). A Zeisel estimation for the pure *O*-methyl compound gave a 98% yield of methyl iodide, and a Herzig–Meyer estimation for the *N*-methyl compound a 95% yield.

The hydroxylepidine (3 g.) was added to 2N-alkali methoxide (9 c.c.) in methyl alcohol (slightly more than 1 equiv.) together with methyl iodide (2·3 c.c.; 1·5 equivs.), and the whole heated under reflux for 30 minutes; a further 3 c.c. of the methoxide solution and 1 c.c. of methyl iodide were then added, and heating was continued for a further 90 minutes. The solution was diluted with water and made strongly alkaline with aqueous sodium hydroxide. The methylation products were extracted

with ether, the extract was dried (Na_2SO_4), the solvent removed, and the solid residue dried in a vacuum-desiccator. The yield of crude ethers was about 80% of the theoretical. The quantities of *O*- and *N*-methyl derivatives were determined as before. The results are given in Table III.

TABLE II.

2N-Alkali.	Expt.	Wt. (g.) of crude methyl compounds from 1·5 g. of triazole.	OMe, %.	NMe, %. found.	NMe, %. corr.	Total OMe and NMe, %.	Ratio, OMe/NMe.	Mean.
LiOH	*a*	1·63	50·0	27·6	45·2	95·2	1·10	1·12
			49·8	26·9	44·1	93·9	1·13	
	b	1·61	50·7	27·6	45·2	95·9	1·12	
			50·7	26·9	44·1	94·8	1·14	
NaOH	*a*	1·60	48·2	31·7	51·9	100·1	0·93	0·97
	b	1·66	47·9	29·9	49·0	96·9	0·98	
	c	1·69	48·0	28·7	47·0	95·0	1·02	
	d	1·10	47·6	30·9	50·6	98·2	0·94	
KOH	*a*	1·28	48·3	28·7	47·0	93·3	0·99	1·01
	b	1·40	48·3	30·0	49·2	97·5	0·98	
	c	1·35	49·0	28·8	47·2	96·2	1·04	
			48·4	28·3	46·4	95·8	1·04	
RbOH	—	—	46·9	24·6	40·0	86·9	1·17	1·17
CsOH	*a*	1·30	49·0	24·3	39·8	88·8	1·23	1·26
			49·2	24·1	39·5	88·7	1·24	
	b	1·22	52·6	25·2	41·3	93·9	1·27	
			51·4	23·8	39·0	90·4	1·32	
$NMeEt_3$·OH	*a*	1·35	54·5	21·0	34·4	88·9	1·58	1·53
			55·8	21·6	35·4	91·2	1·64	
	b	1·20	53·7	22·9	37·5	91·2	1·43	
			57·5	24·1	39·5	97·0	1·46	

TABLE III.

Alkali.	Expt.	OMe, %.	NMe, %.	Ratio, NMe/OMe.	Mean.	Alkali.	Expt.	OMe, %.	NMe, %.	Ratio, NMe/OMe.	Mean.
NaOH	*a*	12·7	52·3	4·12	4·5	KOH	*a*	7·6	82·1	10·8	10·8
	b	21·5	75·7	3·52		$NMeEt_3$·OH	*a*	0	82·6	∞	∞
	c	12·6	71·0	5·63							
	d	15·5	66·5	4·78							

In two qualitative experiments using the tetra-alkylammonium hydroxide no *O*-methyl compound was obtained.

Reimer–Tiemann Reaction.—Phenol (2 g.) was dissolved in approx. 1·5N-alkali (10 c.c.) under a reflux condenser and warmed at 50—60°. Chloroform (3 c.c.) was then added with vigorous shaking which was continued for 15 minutes. The mixture was then heated on a water-bath for 30 minutes. After cooling, the solution, which contained solid, was diluted until the solid dissolved, and then acidified with hydrochloric acid and distilled in steam, about 600 c.c. of distillate being collected. The distillate was transferrred to a graduated flask, concentrated hydrochloric acid added (200 c.c.), and the volume made up to 1000 c.c. with water; 50-c.c. lots were removed, and an equal volume of a solution of 2 : 4-dinitrophenylhydrazine hydrochloride was added. This reagent was prepared by suspending 2 : 4-dinitrophenylhydrazine (4 g.) in dilute hydrochloric acid (25 c.c.), adding concentrated hydrochloric acid (20 c.c.) with shaking and then a further 2 l. of 2N-acid. After being kept overnight the solution was filtered from the small amounts of undissolved material. The precipitated dinitrophenylhydrazone was kept for an hour to coagulate, filtered through a sintered-glass crucible, washed 3 times with 2N-hydrochloric acid, dried for 2 hours at 110°, and weighed. The residue from the steam-distillation was filtered whilst hot, cooled, and made up to 1 l. by concentrated hydrochloric acid (200 c.c.) and water. The *p*-hydroxybenzaldehyde was determined as above in 50-c.c. portions. Similar experiments were performed using 2N-alkali. The results are shown in Table IV.

Kinetic Experiments.—Methyl sulphate was repeatedly shaken with water until the aqueous layer was free from sulphate, dried (Na_2SO_4), and twice distilled at 6—7 mm., the portion boiling at 45—47° being collected. Ethyl sulphate was similarly purified, the fraction boiling at 57·5—60° being collected.

sec.-Butyl hydrogen phthalate and methyl hydrogen phthalate were prepared by the standard method. We are indebted to Dr. J. Kenyon for a specimen of (+)-*sec.*-octyl hydrogen phthalate and to Dr. G. Ader for one of methyl methanesulphonate.

As an example of the technique employed the hydrolysis of methyl sulphate with an equivalent quantity of 0·1N-sodium hydroxide in 50% (v/v) aqueous methyl alcohol at 0° is described.

The methyl sulphate (*ca.* 0·5 c.c.; 1 mol.) was run into a thin, weighed, glass bulb, which was sealed and re-weighed. An amount of the 0·1N-sodium hydroxide solution exactly equivalent (1 mol.) to the methyl sulphate was cooled to 0° and the bulb crushed beneath its surface. After mixing, the solution was transferred to a stoppered flask, cooled in ice–water well stirred with a mechanical stirrer in a large lagged beaker. For experiments at 25° a thermostat was used. From time to time portions (5 c.c.)

of the solution were removed, the reaction was stopped by running the mixture into an equivalent of 0·1N-hydrochloric acid, and the acid formed during hydrolysis titrated against 0·05N-barium hydroxide (bromocresol-purple as indicator). The rate constants were calculated from the usual second-order equation, with results given in Table V.

TABLE IV.

Alkali :	1·5N.				2N.			
	ortho-, %	*para-*, %	*ortho-* : *para-*.	Mean.	*ortho-*, %	*para-*, %	*ortho-* : *para-*.	Mean.
NaOH	12·95	6·38	2·03		5·06	5·69	0·89	
	9·38	4·03	2·33		4·52	5·02	0·90	0·90
	10·95	4·94	2·21	2·08	4·11	4·52	0·91	
	10·25	5·56	1·85					
	8·84	4·44	1·99					
KOH	11·41	9·46	1·21		4·15	4·73	0·877	
	12·24	9·71	1·26	1·24	4·86	5·25	0·923	0·91
	10·79	8·55	1·26		4·90	5·25	0·931	
CsOH	7·35	7·64	0·96	0·98				
	8·19	8·05	1·01					
$NMeEt_3$·OH	3·90	6·43	0·61		2·16	2·43	0·87	0·86
	3·86	6·76	0·57	0·52	1·39	1·63	0·85	
	2·62	6·60	0·40					

TABLE V.

Time, secs., $\times 10^{-3}$.	Titration figures, c.c. (four expts.).				$10^3k^2_{v_0}$, sec.$^{-1}$ (four expts.).			
6	1·4	1·4	1·4	1·4	2·70	2·70	2·70	2·70
12	2·35	2·45	2·35	2·35	2·51	2·70	2·51	2·51
18	3·0	3·2	3·1	3·1	2·36	2·61	2·48	2·48
24	3·8	—	4·05	3·8	2·51	—	2·81	2·51
30	4·45	4·6	4·5	4·45	2·63	2·71	2·71	2·68
36	4·9	4·85	4·8	4·9	2·63	2·60	2·55	2·63
42	5·15	5·1	5·2	5·0	2·50	2·48	2·56	2·56
54	5·8	5·7	5·7	5·9	2·53	2·43	2·43	2·65
66	6·4	6·4	6·5	6·25	2·65	2·66	2·77	2·50
78	6·65	6·7	6·95	6·8	2·51	2·58	2·87	2·71
144	8·0	8·0	8·1	8·2	2·75	2·75	2·90	3·11
258	—	8·7	—	—	—	2·60	—	—
864	10·1	10·05	10·2	10·0				
				Mean :	2·57	2·62	2·66	2·61

Overall mean $k^2_{v_0} = 2·61 \times 10^{-3}$ sec.$^{-1}$.

With 0·1022N-KOH, the overall mean $k_2 = 2·57 \times 10^{-3}$ sec.$^{-1}$ with maximum deviations of +0·23 and −0·14.

With 0·1037N-$NMeEt_3$·OH the overall mean $k_2 = 2·52 \times 10^{-3}$ sec.$^{-1}$ with maximum deviations of +0·10 and −0·17.

TABLE VI.

Time, secs., $\times 10^{-3}$.	Titration figures, c.c. (2 expts.).		$10^3k^2_{v_0}$ sec.$^{-1}$ (2 expts.).	
9	0·85	0·9	7·36	8·13
18	1·55	1·65	8·60	8·7
27	1·95	2·2	7·33	8·6
36	2·4	2·7	7·25	8·5
45	2·8	2·9	7·15	7·5
54	3·5	3·35	8·28	7·7
90	4·25	4·55	6·63	7·4
124·5	5·3	5·4	6·98	7·15
166·2	6·2	5·95	7·13	6·71
364	10·2	10·4		
		Mean :	7·41	7·70

The hydrolysis of ethyl sulphate was investigated at 0° with 1·5 equivalents of alkali in 90% (v/v) aqueous methanol. With 1·0328N-sodium hydroxide the results given in Table VI were obtained.

The deviation from the mean $k^2_{v_0}$ is as much as 16% but, as the concentrations were high and appreciable errors were likely owing to volume changes in mixing and to separation of solid sodium ethyl sulphate during the reaction, it was considered that the results were as satisfactory as could be expected.

With 1·0328N-potassium hydroxide the mean $k^2_{v_0} = 9·5 \times 10^{-4}$ sec.$^{-1}$ with maximum deviations of +0·6 and −0·5, and with 1·0534N-$NMeEt_3$·OH $k^2_{v_0} = 10·9 \times 10^{-3}$ sec.$^{-1}$ with maximum deviations of +1·2 and −1·8.

The maximum value for sodium hydroxide was A_0^{25} 8·7, and the minimum for potassium hydroxide was 9·0; it is thus uncertain whether there is any appreciable difference between these two alkalis, but the minimum for methyltriethylammonium hydroxide was A_0^{25} 15·1, which is about 1·75 times the maximum for sodium hydroxide and beyond the limit of experimental error.

Methyl methanesulphonate was added to an equivalent quantity of 1·026N-alkali and the reaction carried out in a thermostat at 25°. Portions (2 c.c.) were removed at intervals, run into ice-cold water (20 c.c.), and titrated against 0·0989N-hydrochloric acid (bromocresol-purple). Results are in Table VII.

TABLE VII.

1·026N-NaOH.			1·026N-$NMeEt_3$·OH.		
Time, secs., $\times 10^{-3}$.	Titre.	$10^4A_0^{25}$, sec.$^{-1}$.	Time, secs., $\times 10^{-3}$.	Titre.	$10^4A_0^{25}$, sec.$^{-1}$.
3·6	16·3	5·08	3·8	14·7	(8·35)
7·3	14·0	5·30	7·35	11·6	9·30
11	12·3	5·34	11	9·7	9·35
14·6	10·8	5·58	14·65	8·3	9·40
18·45	9·8	5·45	18·55	7·2	9·44
24	8·4	5·62	24	6·1	9·38
33	6·95	5·61	32·95	4·8	9·57
51	5·15	5·63	51·1	3·4	9·58
87	3·35	5·73	87	2·2	9·34
159	2·0	5·69	684	0·2	0·2
3 days	0·0				
	Mean:	5·5		Mean:	9·4

A weighed quantity of alkyl hydrogen phthalate was dissolved in exactly 2 equivalents of aqueous alkali, one being required to form the salt with the free carboxyl group, and the reaction carried out in a thermostat at 25°. Portions (2 c.c.) were removed at intervals, diluted with water (20 c.c.), and titrated against 0·1N-hydrochloric acid (phenolphthalein). (+)-*sec.*-Octyl hydrogen phthalate with 1·026N-sodium hydroxide gave a mean A_0^{25} 6·2 $\times 10^{-4}$ sec.$^{-1}$ with maximum deviations of +0·3 and −0·4. With 1·026N-$NMeEt_3$·OH $A_0^{25} = 6{\cdot}95 \times 10^{-4}$ sec.$^{-1}$ with maximum deviations of +0·4 and −0·2. The rate constants, in view of the degree of accuracy, are too similar for a decision whether the difference is significant, especially as a complication arose owing to separation of octyl alcohol during the reaction.

sec.-Butyl hydrogen phthalate and methyl hydrogen phthalate were hydrolysed under similar conditions. Results are given in the Introduction.

The hydrolyses in 90% (v/v) methyl alcohol were carried out as in aqueous solution, a weighed quantity of the ester being dissolved in two equivalents of alkali in aqueous methyl alcohol and kept at 25°. With sodium hydroxide, solid sodium phthalate began to separate after about 8 hours and the values of the rate constants were not very concordant; this did not occur with potassium hydroxide or with methyltriethylammonium hydroxide. The results for *sec.*-butyl hydrogen phthalate are given in Table VIII.

TABLE VIII.

1·047N-NaOH.		0·985N-KOH.		1·077N-$NMeEt_3$·OH.	
Time, hours.	$10^4A_0^{25}$, sec.$^{-1}$.	Time, hours.	$10^4A_0^{25}$, sec.$^{-1}$.	Time, hours.	$10^4A_0^{25}$, sec.$^{-1}$.
2	1·25	2	1·00	2 }	practically no
3	1·16	3	0·91	3 }	reaction
12·25	1·66	7	1·09	12·25	(0·041)
26·33	1·77	20·33	1·16	26·33	0·091
31·5	1·93	26·33	1·19	31·5	0·094
61·2	1·39	31·5	1·14	61·2	0·097
81·5	1·30	55·66	1·14	81·5	0·089
108	1·16	92	1·05	108	0·091
146	1·09			146	0·097
193·5	1·03			193·5	0·097
Mean:	1·38	Mean:	1·08	Mean:	0·093

With methyl hydrogen phthalate and sodium hydroxide, over the range 15—315 minutes, whereafter large amounts of sodium phthalate had separated, the mean A_0^{25} was 1·25 $\times 10^{-4}$ sec.$^{-1}$ with maximum deviations of ±0·3, and with methyl hydrogen phthalate and methyltriethylammonium hydroxide over the range 35—4440 minutes, the mean A_0^{25} was 0·14 $\times 10^{-4}$ sec.$^{-1}$ with a maximum deviation of ±0·01.

Methyl acetate in 90% (v/v) methyl alcohol was hydrolysed at 0° with 1·033N-alkali. Over the range 15—240 minutes with sodium hydroxide A_0^0 was 1·6 $\times 10^{-4}$ sec.$^{-1}$ with a deviation of ±0·2, with potassium hydroxide 1·7 $\times 10^{-4}$ sec.$^{-1}$ with a deviation of +0·3 and −0·2, and with methyltriethylammonium hydroxide 1·1 $\times 10^{-4}$ sec.$^{-1}$ with a deviation of +0·1 and −0·2.

THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON.

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153. *The Mechanism of Decarboxylation. Part V. Kinetics of the Decarboxylation of Hydroxybenzoic Acids.*

By B. R. Brown, D. Ll. Hammick, and A. J. B. Scholefield.

The rates of decarboxylation of salicylic, 2 : 4-dihydroxybenzoic, and 2 : 4 : 6-trihydroxybenzoic acids have been measured in resorcinol solution over a temperature range of 110—240°. The fall in activation energies (increase in rate) with increase in *o*- and *p*-substitution by hydroxyl groups supports the conclusion that with these acids the decarboxylation is an S_N2 mechanism. The Hinshelwood–Fairclough relation between $\log_{10} PZ$ and $1/E$ is obeyed.

Recently Schenkel and Schenkel-Rudin (*Helv. Chim. Acta*, 1948, **31**, 514) suggested that decarboxylation may occur by two mechanisms, analogous to the S_N1 and S_N2 replacement reactions of Hughes and Ingold (*J.*, 1935, 244):

$$S_N1 \qquad R{\cdot}CO_2^- = R^- + CO_2$$
$$S_N2 \quad H^+ + R{\cdot}CO_2^- = HR + CO_2$$

Substantial evidence for the S_N1 mechanism is available (*e.g.*, Pedersen, *J. Physical Chem.*, 1934, **38**, 559; Verhoek, *J. Amer. Chem. Soc.*, 1939, **61**, 186; Parts I, II, III, and IV of this series, Hammick *et al.*, *J.*, 1937, 1724; 1939, 809; 1949, 173 and 659). Examples of the S_N2 mechanism are rapidly accumulating (Schubert, *J. Amer. Chem. Soc.*, 1949, **71**, 2639; Johnson and Heinz, *ibid.*, p. 2913).

The S_N2 mechanism will be facilitated by a high electron density on the carbon atom next to the carboxyl group. Moreover, since the mechanism is essentially bimolecular and involves an acid molecule and a solvated proton, acids which are decarboxylated in this manner will be stable in alkaline but unstable in acid solution. Support for this view is found in the semi-quantitative results of Cazeneuve (*Bull. Soc. chim.*, 1896, **15**, 73) and of Hemelmeyr (*Sitz. Akad. Wiss. Wien*, 1912, **121**, 1359), who show that *o*- and *p*-hydroxybenzoic acids behave thus. The *m*-hydroxybenzoic acids, however, in which the hydroxyl groups cannot make any appreciable contribution to the electron density on the carbon atom next to the carboxyl group, are stable even in acid solution. The suggestion that the decarboxylation of *o*- and *p*-hydroxybenzoic acids may occur by a bimolecular mechanism involving attack of a proton on the negative α-carbon atom has also been made by Fieser and Fieser ("Organic Chemistry," D. C. Heath and Co., Boston, 1944, p. 674).

The aim of the kinetic work here presented was to study the effect of the successive substitution of hydroxyl groups into the *o*- and *p*-positions of benzoic acid on the rate of decarboxylation in resorcinol, which was selected as solvent for reasons given in the Discussion below. The work of Hinshelwood, Laidler, and Timm (*J.*, 1938, 848) indicates that a comparison of activation energies with type and amount of substitution should provide evidence for or against an S_N2 mechanism.

Experimental.

Materials.—Salicylic acid was crystallised twice from water and had m. p. 156°. 2 : 4-Dihydroxybenzoic acid (β-resorcylic acid) was crystallised three times from water and had m. p. 216°. 2 : 4 : 6-Trihydroxybenzoic acid was crystallised once from alcohol and twice from ether and had m. p. 189°.

The solvent, resorcinol, was distilled at atmospheric pressure, and had b. p. 276°, m. p. 110°.

Apparatus.—The method used to follow the reaction was by measurement of evolved carbon dioxide, at room temperature and pressure. The apparatus of Walton (*Z. physikal. Chem.*, 1904, **47**, 185) was modified for use at high temperatures (110—240°) and was very similar to the apparatus used by Schubert (*loc. cit.*). Temperature control was obtained by immersing the reaction vessel (containing about 0·3 g. of acid in 10 g. of resorcinol) in a lagged vapour-bath containing a suitable liquid boiling under reflux at the prevailing atmospheric pressure. Temperatures constant to ±0·1° could be maintained for at least 4 hours. The bath liquids were distilled at atmospheric pressure, and fractions boiling over 0·2° were used to construct the Arrhenius plots. The hot solvent (resorcinol) was saturated with carbon dioxide before measurements were made.

The main source of error was likely to arise from variation of the temperature gradient between the evolved carbon dioxide (at the temperature of the reaction) and the measuring burette (at room temperature). This was minimised by using a standard procedure, and by protecting the connecting tubes from temperature changes.

Results.—Since the system had to be stabilised before readings were taken, it was impracticable to obtain an accurate value for the initial concentration of the acid. Moreover, it was inconvenient to prolong the decarboxylation in order to read the total volume of carbon dioxide evolved at the completion of the reaction. These difficulties were overcome by using the method of plotting devised by Guggenheim (*Phil. Mag.*, 1926, **2**, 538). Two series of values for the volume of carbon dioxide evolved, v and v', separated by a time interval t, are obtained. A plot of $\log_{10}(v' - v)$ against time yields a line of gradient $-0{\cdot}434k$, where k is the velocity constant for the decarboxylation at the

temperature used. A typical series of results is shown in Table I. The observed values of $\log_{10}(v' - v)$ are compared with those calculated from the equation to the line of gradient $-0{\cdot}434k$.

TABLE I.

Decarboxylation of 2 : 4-*dihydroxybenzoic acid in resorcinol (at* 465·2° K.)

Time (sec.).	v (ml.).	v' (ml.).	$(v' - v)$ (ml.).	$\log_{10}(v' - v)$ (obs.).	$\log_{10}(v' - v)$ (calc.).
300	5·9	26·4	20·5	1·311	1·325
450	10·0	27·5	17·5	1·243	1·242
600	14·0	28·3	14·3	1·155	1·158
750	17·2	29·0	11·8	1·072	1·074
900	19·8	29·6	9·8	0·991	0·991
1050	21·9	30·1	8·2	0·914	0·908
1200	23·7	30·5	6·8	0·833	0·824
	t = 1200 sec.			$k = 12{\cdot}8 \times 10^{-4}$ sec.$^{-1}$.	

Four determinations of k at this temperature yielded the values $k = 11{\cdot}0$, 12·8, 14·0, and $14{\cdot}6 \times 10^{-4}$ sec.$^{-1}$. Average $k = 13{\cdot}1 \times 10^{-4}$ sec.$^{-1}$.

A plot of $1/T$ and $\log_{10} k$ (from Table II) gives the results collected in Table III.

TABLE II.

Effect of temperature.

o-Hydroxybenzoic acid.		2 : 4-Dihydroxybenzoic acid.		2 : 4 : 6-Trihydroxybenzoic acid.	
°K.	10^4k.	°K.	10^4k.	°K.	10^4k.
479·7	1·32	453·6	5·65	382·7	15·4
489·8	2·53	454·2	6·61	383·2	17·9
491·5	3·15	455·4	7·41	384·1	18·3
492·7	3·25	465·2	13·1	391·0	24·2
493·0	3·53	468·4	16·2	396·7	29·5
496·2	3·96	471·1	20·4	397·7	36·7
497·2	5·02	478·2	31·1		
508·2	8·95	480·3	36·7		
509·2	10·5				

TABLE III.

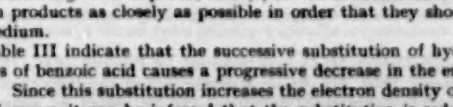
Acid.	E (cals.).	$10^3/E$.	$\log_{10} PZ$ (from k in sec.$^{-1}$).
Benzoic	>39,000 *	—	—
o-Hydroxybenzoic	33,600	5·46	11·5
2 : 4-Dihydroxybenzoic	29,200	5·85	10·9
2 : 4 : 6-Trihydroxybenzoic	13,600	8·68	5·0

* Estimated from the observation that benzoic acid is undecomposed at 250° in resorcinol.

DISCUSSION.

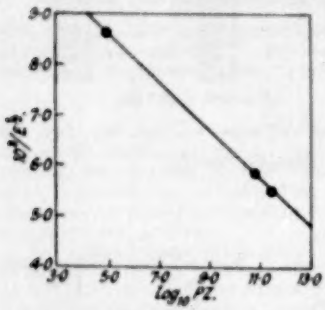
The solvent resorcinol was chosen for these measurements for the following reasons: (1) the solvent had to be acidic in order that the bimiolecular S_E2 reaction would show pseudo-first-order kinetics, owing to the presence of a constant excess of acidic molecules, (2) the solvent had to be the same for each acid in order to give comparable results, hence a solvent liquid over a wide temperature range was required, and (3) it was desirable that the solvent should resemble the reaction products as closely as possible in order that they should cause the least possible change in medium.

The results in Table III indicate that the successive substitution of hydroxyl groups into the *o*- and *p*-positions of benzoic acid causes a progressive decrease in the energy of activation for decarboxylation. Since this substitution increases the electron density on the carbon atom next to the carboxyl group, it can be inferred that the substitution is reducing the repulsion between an attacking solvated proton and the acid molecule (cf. Hinshelwood, Laidler, and Timm, *loc. cit.*). The occurrence of this effect is consistent with the S_E2 mechanism:



The remarkable drop in the *PZ* factor (of the equation $k = PZ \cdot e^{-E/RT}$) on passing from 2 : 4-dihydroxy- to 2 : 4 : 6-trihydroxy-benzoic acid is perhaps to be associated with a steric effect of the second *o*-hydroxyl group in inhibiting the approach of the solvated proton.

The view that decarboxylation can take place by an S_E2 mechanism involving the attack of a solvated proton on the α-carbon atom is supported by kinetic studies on anthracene-9-carboxylic acid (Schenkel and Schenkel-Rudin, *loc. cit.*), certain cinnamic acids (Johnson and Heinz, *loc. cit.*), mesitoic acid (Schubert, *loc. cit.*), and on the *o*- and *p*-hydroxybenzoic acids. However, these authors put forward no evidence, nor have we been able to obtain any, as to the precise nature of the carboxylic entity which suffers reaction, *i.e.* to distinguish between (1) and (2) :



(1) $SH^+ + R{\cdot}CO_2^- = RH + S + CO_2$
(2) $SH^+ + R{\cdot}CO_2H = RH + S + CO_2 + H^+$

On the other hand, studies of S_E1 decarboxylations have always indicated that the carboxyl group is in the anionic form before decarboxylation :

$$R{\cdot}CO_2^- = R^- + CO_2$$

In order to clarify the details of the S_E2 mechanism further experiments are clearly required.

Hinshelwood and Fairclough (*J.*, 1937, 538, 1573) advance theoretical reasons for the expectation of a linear relationship between $1/E^{\frac{1}{2}}$ and $\log_{10} PZ$ in a series of closely related reactions. The accompanying figure indicates that such a relationship holds for the decarboxylation of hydroxybenzoic acids. This result is interesting on account of the large range of *E* and *PZ* values covered by our data, and on account of the value $-0{\cdot}21 \times 10^4$ found for the slope of the line, $d(\log_{10} PZ)/d(1/E^{\frac{1}{2}})$, which is very close to that found by Hinshelwood and Fairclough (*loc. cit.*) for several reactions.

Dyson Perrins Laboratory, Oxford University. [*Received, November 5th*, 1949.]

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154. *Mechanism of the Molecular Rearrangement produced by the Action of Alkali on Chloral-quinaldine* [2-(3 : 3 : 3-*Trichloro-2-hydroxypropyl*)-*quinoline*].

By B. R. Brown, D. Ll. Hammick, and Sir Robert Robinson.

It is shown that the re-arrangement named in the title is equivalent to an αγ-change of a substituted 1-*o*-aminobenzylideneпropanone to a substituted 3-*o*-aminobenzylideneпropanone. This statement is only intended as a description of the basic change in the carbon skeleton and it does not represent the authors' view of the actual mechanism of the process.

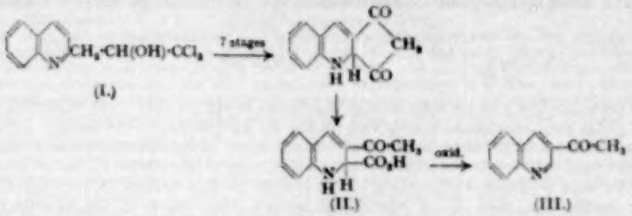
2 : 3-Dimethylquinoline was condensed with chloral and the adduct treated with aqueous-alcoholic sodium hydroxide.

The main product was the normal methylquinolylacrylic acid but oxidation of the coloured material in the mother-liquor afforded 3-quinolyl ethyl ketone in small yield.

An orange salt, $C_{13}H_{10}O_2NNa,3H_2O$, was obtained by Einhorn (*Ber.*, 1886, **19**, 904; Einhorn and Sherman, *Annalen*, 1895, **287**, 38) as a by-product of the hydrolysis of chloral-quinaldine [2-(3 : 3 : 3-trichloro-2-hydroxypropyl)quinoline] (I) by means of aqueous alcoholic sodium hydroxide. It was oxidised *via* a carbonyl compound to an acid which was much later proved by Borsche and Manteuffel (*Annalen*, 1936, **526**, 22) to be quinoline-3-carboxylic acid.

A molecular rearrangement at some stage was thus revealed but the German workers did not follow up the implications. Woodward and Kornfeld (*J. Amer. Chem. Soc.*, 1948, **70**, 2508) showed that the carbonyl compound obtained by oxidation of the orange sodium salt is 3-quinolyl methyl ketone (III) and made it very probable that the Einhorn salt is a dihydroquinoline

derivative (cf. II). Their view (*A*) of the mechanism of the process is schematically illustrated below.

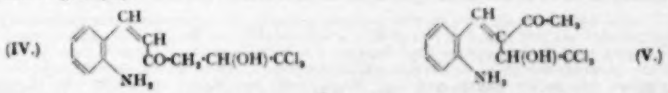


An alternative hypothesis (*B*) was considered by Woodward and Kornfeld but was rejected for good reasons. This involved the disruption of (I) into *o*-aminobenzylideneacetone and chloral, or their equivalents, and recombination of these elements of the structure in a new position.

In the particular case of chloral-quinaldine this allows of an intermediate stage identical with a possibility in our own hypothesis (*C*, below), but this is derived in a different manner and would not give the same results, for example in an investigation with labelled atoms.

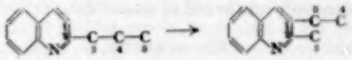
Our interest in this subject arose from the fact that we found Woodward and Kornfeld's theoretical explanations unconvincing, especially that advanced to justify the assumption of the formation of the *cyclo*pentane ring of a postulated intermediate by attack on the β-position of the quinoline nucleus. This seemed to overlook the much greater probability of the formation of a pyrrolidine ring, if cyclisation were to occur at all.

The view (*C*) of the rearrangement which appeared most acceptable to us can best be explained didactically by noting that chloral-quinaldine by imaginary hydrolytic fissions would yield the unsaturated ketone (IV) which is the 1-*o*-aminobenzylidene derivative of $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH(OH){\cdot}CCl_3$. We suggest that the *o*-aminobenzylidene group is transferred from the 1- to the 3-position in the pentanone chain. This gives (V) which is dehydrated and hydrolysed to give (II).

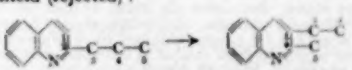


It would be of interest to study the rearrangement by means of labelled carbon atoms and the following scheme shows what results are to be expected on the basis of the three hypotheses (*A*), (*B*), and (*C*).

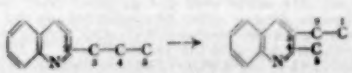
(*A*) Woodward and Kornfeld (favoured):



(*B*) Woodward and Kornfeld (rejected):



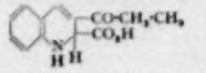
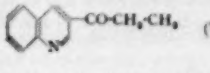
(*C*) Present authors:



It will be noticed that (*A*) could readily be distinguished from (*B*) and (*C*) by the isotope method but that a distinction between (*B*) and (*C*) would require a quinaldine labelled at the methyl group or at the carbon atom in the 3-position of the quinoline nucleus, but not at both points simultaneously in the same way. The slight preparative difficulty so indicated can best be overcome by a quinaldine synthesis from quinoline.

In the meantime the hypothesis (*C*) is seen to be in harmony with the results obtained by Woodward and Kornfeld with related substances in the quinoline and pyridine series.

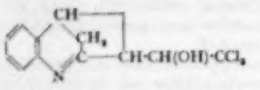
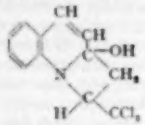
According to hypotheses (*A*) and (*B*), 2 : 3-dimethylquinoline-chloral could not undergo the rearrangement but if (*C*) is correct we could obtain (VI) and by oxidation 3-quinolyl ethyl ketone (VII). Actually the colour change indicates that the reaction proceeds as expected, but

(VI.)   (VII.)

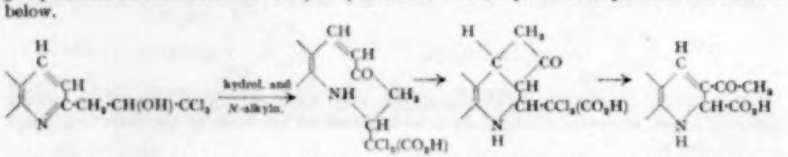
the yield is certainly low and we were unable to isolate the salt of (VI). On oxidation, a small amount of (VII) was isolated and identified as the 2 : 4-*dinitrophenylhydrazone*. The ketone (VII) was synthesised by an unambiguous method described in the Experimental section. We are fully convinced that this result establishes the correctness of hypothesis (*C*) but in view of the small yield we hope to obtain confirmation by the isotope method applied to the original case.

On the assumption that (*C*) is essentially correct, the stages of the process call for consideration. We do not favour a theory of fission and recombination of the parts; it seems almost certain that the molecule undergoes a change somewhat similar to that which may be postulated for the ring-enlargement of pyrrole to 3-chloropyridine :

In the quinaldine-chloral case, two four-ring intermediates are plausible (VIII and IX) :

(VIII.)   (IX.)

These represent two parts of the completed rearrangement, and the third is hydrolysis of the imine linkage. These three elements occur in undetermined succession but, since the benzylidene group should be more active after hydrolysis of the imine, a probable sequence is that shown below.



The formation of a four-ring and other precisions of this scheme are not necessary to our theory which can be interpreted with the aid of several different detailed mechanisms.

Experimental.

Ethyl 3-*Propionylquinaldate*.—A mixture of *o*-aminobenzaldehyde (3·9 g.), ethyl propionylpyruvate (5·6 g.) (Diels, Sielisch, and Möller, *Ber.*, 1906, **39**, 1333), alcohol (50 ml.), and potassium hydroxide (0·05 g.) was boiled under reflux for 10 hours. Colourless, slender needles (3·2 g.) separated from the cooled reaction mixture. A further 1·2 g. were obtained by dilution of the mother-liquor with water. *Ethyl* 3-*propionylquinaldinate* separated from alcohol as colourless needles, m. p. 107—108° (Found : C, 70·2; H, 5·8. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·8%).

3-*Propionylquinaldic Acid*.—The above ester (1·1 g.) was heated on the steam-bath with water (50 ml.) and potassium hydroxide (2·0 g.). After ½ hour the hot solution was filtered and acidified with dilute sulphuric acid. Slender, colourless needles (0·9 g.) separated on cooling. Recrystallisation from water yielded 3-*propionylquinaldic acid* as colourless needles, m. p. 153° (decomp.) (Found : C, 67·9; H, 4·8. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8%). The acid forms a very sparingly soluble, pale green copper salt.

3-*Quinolyl Ethyl Ketone* (VII).—3-Propionylquinaldic acid (2·3 g.) was refluxed with moist aniscle (20 ml.) until decarboxylation was complete (3 hours). The mixture was extracted with 10% hydrochloric acid and benzene, and the acid layer was basified, giving a colourless oil which quickly solidified. The dry solid (1·8 g.) was crystallised from light petroleum (b. p. 60—80°) and then from aqueous methanol, from which it separated as silky, colourless needles, m. p. 79—80° (Found : C, 77·6; H, 5·9. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine–alcohol as deep orange-red needles, m. p. 248—249° (Found : C, 59·6; H, 4·0; N, 19·5. $C_{18}H_{15}O_4N_5$ requires C, 59·2; H, 4·1; N, 19·2%).

3-*Methyl*-2-(3 : 3 : 3-*trichloro*-2-*hydroxypropyl*)*quinoline*.—A mixture of 2 : 3-dimethylquinoline (6·0 g.), chloral (6·0 g.), and pyridine (6·0 ml.) was heated on the steam-bath for 2 hours. The solid obtained by addition to water was washed free from pyridine and recrystallised several times from 75% aqueous alcohol, to yield the *adduct* (9·0 g.) as colourless needles which, dried at 80° in a vacuum, had m. p. 134—135° (Found: N, 4·7. $C_{12}H_{12}ONCl_3$ requires N, 4·6%).

Action of Alkali on 3-*Methyl*-2-(3 : 3 : 3-*trichloro*-2-*hydroxypropyl*)*quinoline*.—A suspension of the quinoline derivative (15·5 g.) in a hot mixture of alcohol (60 ml.) and water (50 ml.) was treated rapidly with aqueous sodium hydroxide (10 g. in 35 ml. of water). The resulting clear orange-yellow solution was evaporated to dryness, and the solid sodium salts were dissolved in a little water and treated with a slight excess of acetic acid to liberate a mixture of crude brown acids. Treatment of this mixture with concentrated hydrochloric acid (15 ml.) and filtration gave a pale brown residue (11·5 g.) and a deep brownish-red filtrate. Crystallisation of the solid from alcohol yielded the *β-(3-methyl-2-quinolyl)-acrylic acid hydrochloride* as slightly yellow, opaque laminæ, m. p. 220° (decomp.) (Found: N, 5·1. $C_{13}H_{11}O_2N,HCl,C_2H_6O$ requires N, 5·0%). Partial neutralisation with aqueous sodium carbonate and crystallisation from aqueous alcohol yielded *β-(3-methyl-2-quinolyl)acrylic acid* as colourless needles, m. p. 173—178° (decomp.) (Found: C, 72·8; H, 5·2. $C_{13}H_{11}O_2N$ requires C, 73·3; H, 5·2%).

The deep brownish-red filtrate was nearly neutralised with sodium carbonate, and the dark brown solid separated, washed with water, and dried (0·4 g.). This mixture of acids was dissolved in dilute acetic acid, and air was bubbled through the solution for 11 days, during which the colour faded appreciably. The solution was made alkaline with aqueous sodium hydroxide, and the basic products were taken up in ether. Evaporation of the ether left a small amount of oil, which was dissolved in alcohol and treated with alcoholic 2 : 4-dinitrophenylhydrazine sulphate. The orange-red solid (0·1 g.) which separated was twice crystallised from alcohol–pyridine, from which it separated as deep orange-red micro-needles, m. p. 247—248° (Found: C, 59·8; H, 4·1; N, 18·5. Calc. for $C_{19}H_{14}O_5N_4$: C, 59·2; H, 4·1; N, 19·2%). The m. p. was not depressed on admixture with a specimen of the 2 : 4-dinitrophenyl hydrazone of 3-quinolyl ethyl ketone, prepared as described above. A comparison of the behaviour of the two specimens with solvents and in habit of crystallisation confirmed their identity.

The 2 : 4-*dinitrophenylhydrazone* of 3-quinolyl methyl ketone separated from nitrobenzene as minute red prisms, m.p. 261—262° (Found: C, 58·1; H, 3·7. $C_{17}H_{12}O_4N_4$ requires C, 58·2; H, 3·7%). Mixed with the above dinitrophenylhydrazone from 2 : 3-dimethylquinoline, the m. p. was depressed to 242—246°.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October 20th*, 1949.]

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155. *Polarographic Reduction of Some Heterocyclic Molecules. Part I. The Reduction of Cinchoninic Acid.*

By D. J. CASIMIR and L. E. LYONS.

Cinchoninic acid is reduced at the dropping-mercury cathode over the pH range 1—13. The mechanism differs with the pH but in every case a total of two hydrogen ions and two electrons is used for each molecule. Waves with $n = 2$ occur in both extremes of pH, but around the neutral point the reduction proceeds in two separate stages, each involving one electron. As the slopes of the waves on logarithmic analysis do not give simple values the theory of van Rysselberghe has been tested but found to fail. Acid conditions are most suitable for the determination of cinchoninic acid.

THE polarographic reduction of quinoline-2- and -8-carboxylic acids has been studied by Stock (*J.*, 1944, 427; 1949, 586). The detailed mechanism still remains in some doubt. The behaviour of quinoline-4-carboxylic acid is now reported and discussed. All work was done on well-buffered aqueous solutions, at 25·0° generally, from pH 1 to pH 13; potentials are referred to the saturated calomel electrode at 25°. The concentration used was, unless otherwise specified, $2{\cdot}00 \times 10^{-3}$ M. The present work is part of a wider study which should complement that of Stock.

The reduction of cinchoninic acid gives waves over the entire pH range: at pH 1—8 a single wave, *A*, which at pH 8—11 is replaced by two waves, *B* and *C*, each half the height of *A*. At still higher pH's the curve is once more a single wave, *D*, similar to *A* in height. As the pH rises the reduction becomes more difficult and the curves are displaced to more negative potentials. Typical waves are shown in Fig. 1. The lowering of hydrogen overvoltage was observed, as is usual with quinoline derivatives (cf. Stock, *J.*, 1949, 763), but in this case was not sufficient to interfere with the reduction curve even at pH 1·3. In addition to the main waves pre-steps to *A* and *D* were observed (see below). Maxima were eliminated by the use of gelatin. These pre-steps occurred around pH 7 but only to a much less extent than with quinaldinic acid. Some minor aberrations from a smooth form were observed near the neutral point.

The half-wave potential, $E_{\frac{1}{2}}$, of wave *A* was a linear function of pH, and for pH <8 is given by $E_{\frac{1}{2}} = -(0{\cdot}550 + 0{\cdot}068\ \mathrm{pH})$ volts. This same equation applies to $E_{\frac{1}{2}}$ of wave *B* when pH is >8. Fig. 2 shows $E_{\frac{1}{2}}$–pH relationships for all waves. $E_{\frac{1}{2}}$ of *C* and *D* appeared independent of pH.

The wave-heights when plotted against pH showed that waves *A* and *D* were of approximately constant height (11·1 μa.) for pH 1—8 and pH >11 respectively, while *B* and *C* were constant at 5·3 μa. for pH 8—11, for the given capillary characteristics. In order to compare one compound with another examined on a different set-up it is necessary to eliminate the latter factor; consequently, a plot of pH against the wave-height divided by $m^{2/3}t^{1/6}$ is shown in Fig. 3, the wave-height having been corrected for variations in residual current and in drop-time variation with electrode potential. It is suggested that such a plot should become standard in future polarographic studies rather than a plot of pH against wave-height in μa.

Fig. 1.

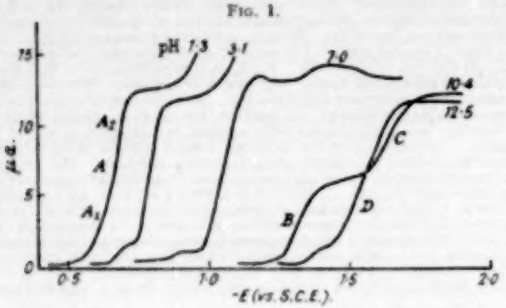


Fig. 2.

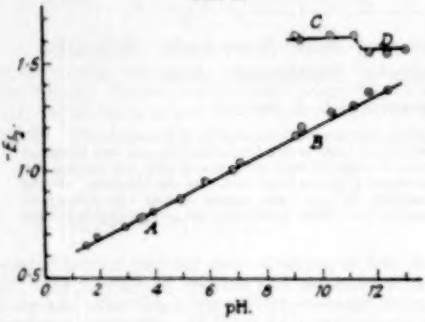
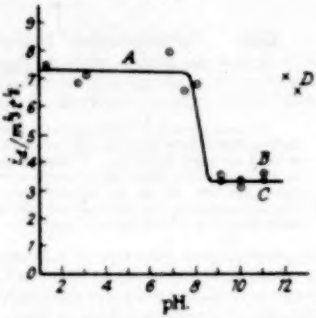


Fig. 3.

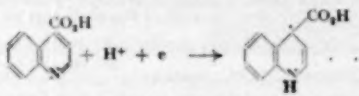


The number, *n*, of electrons per molecule concerned in the reduction process at each diffusion-controlled wave may be estimated from Ilkovic's equation $n = i_d/605D^{\frac{1}{2}}Cm^{2/3}t^{1/6}$, where i_d is the diffusion current in μa., *D* the diffusion coefficient in $cm.^2 sec.^{-1}$, *C* the concentration of the reducible substance in millimoles/l., *m* the mg. of mercury dropping per second, and *t* the drop-time in seconds. Taking the value of *D* to be the same as that of quinaldinic acid, $0{\cdot}80 \times 10^{-5}$ $cm.^2 sec.^{-1}$ (Stock, *loc. cit.*), the following (nearest integer) values were obtained: *A*, $n = 2$; *B*, $n = 1$; C, $n = 1$; *D*, $n = 2$. With the reverse procedure, assuming the value of *n* to be exactly either 2 or 1, the mean value of the diffusion coefficient was $0{\cdot}88\ (\pm 0{\cdot}04) \times 10^{-5}$ $cm.^2 sec.^{-1}$, to be compared with quinoline-2-carboxylic acid $0{\cdot}80 \times 10^{-5}$ (from conductivity data), quinoline-8-carboxylic acid $0{\cdot}92 \times 10^{-5}$, and 8-hydroxyquinoline $0{\cdot}85 \times 10^{-5}$ (both from polarography).

The plots of $\log i/(i_d - i)$ against *E* were generally linear for *E* near $E_{\frac{1}{2}}$, but the slopes varied from curve to curve. Thus for wave *A* slopes of 0·062, 0·070, 0·079, 0·082, 0·084, and 0·086 were obtained. Exclusion of a section of wave *A* which seemed possibly to overlie a pre-step lowered these values, *e.g.*, from 0·062 to 0·051. For a two-electron process the corresponding slope for a "reversible" reaction equals 0·030, and for a one-electron process 0·059. The discrepancy between 0·030 and the observed values might, it was thought, be explicable by the

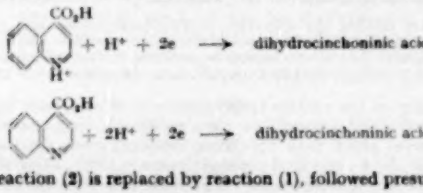
theory of van Rysselberghe (*J. Amer. Chem. Soc.*, 1946, **68**, 2047). This theory attempts to explain the departure of certain polarographic curves from the reversible reaction slope in terms of a Freundlich adsorption isotherm for the product of the electrode reaction. The theory is not applicable if the half-wave potential varies markedly with either temperature or concentration of the reducible substance. For cinchoninic acid, experimentally $E_{\frac{1}{2}} = 0{\cdot}795$ v. at 25°, 0·787 v. at 35°, and 0·793 v. at 45° (all compared to S.C.E. at 25°; $c = 2{\cdot}00 \times 10^{-4}$ M.; pH 3·55). Also $E_{\frac{1}{2}} = 0{\cdot}795$ v. for $2{\cdot}00 \times 10^{-4}$ M., and 0·792 v. for $1{\cdot}00 \times 10^{-4}$ M. (25°; pH 3·55). The value of $E_{\frac{1}{2}}$ in every case was obtained from a curve which had been corrected for residual current (cf. Delahay, *Rec. Trav. chim.*, 1948, **67**, 159) and for the iR drop across the cell (R being measured each time using A.C.). Thus the van Rysselberghe theory might be thought applicable. Under our conditions the theory gives rise to the relation $dE/di = 0{\cdot}051x$, where x = the number of molecules which react with two hydrogen ions and two electrons. The number of electrons reacting with each molecule reduced is thus $2/x$. Measurement of dE/di for wave A gave x values in eleven different cases ranging from 1·8 to 3·6 with an average of 2·6. It follows that n obtained from the Ilkovic equation differs from that obtained from the van Rysselberghe theory by a factor of more than two. Thus the theory seems not to be of general applicability.

The variation in ultra-violet absorption spectrum with pH has been studied for quinaldinic acid (Lyons, *Proc. Roy. Soc. N.S.W.*, in the press), the polarography of which resembles that of cinchoninic acid. From this and other evidence there is no doubt that at pH $\leqslant 4$ the latter is present in the form containing H^+ on the nitrogen atom. Further evidence may be obtained from the polarography of 8-hydroxyquinoline (Stock, *loc. cit.*), where the $E_{\frac{1}{2}}$–pH plot of (Stock's) wave B shows an inflection at pH 5·3, although his larger wave A, which may be considered analogous to A of the present paper, shows no such inflection. Casimir and Lyons (unpublished) obtained such an inflection for quinoline itself, but here wave A seems to correspond to a one-electron process (resembling 8-hydroxyquinoline but not the 2- or 4-carboxylic acids). All this, and the fact that the $E_{\frac{1}{2}}$–pH plot (Fig. 2) for cinchoninic acid shows no inflection about pH 5, means that the first half (A_1) of A may *not* be identified in origin with B which is attributable to

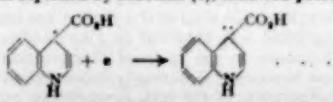


(1)

But to connect A_1 with the addition of only a single electron to $\equiv NH^+$ as the potential-determining step is not valid as the half-wave potential of A_1 varies with pH. All that can be done at the present stage of theory is to associate the whole wave A with reaction (2a) when pH < pK, and with reaction (2b) when pH > pK < 8 (K ≡ dissociation constant of the base).



For pH > 8 < 11 reaction (2) is replaced by reaction (1), followed presumably by



(3)

which may then react with water to give the dihydro-compound. It may be possible to verify reaction (3) by theoretical calculations after the method of Maccoll (*Nature*, 1949, **163**, 178). Reaction (3) may be associated with wave C. The fact that $E_{\frac{1}{2}}$ of C is independent of pH supports the mechanism.

For pH >11 the potential-determining step must consist solely of the addition of two electrons, in order that $E_{\frac{1}{2}}$ of D be independent of pH, the product ion reacting to give the dihydro-compound. In each instance formation of the latter would be followed by di- or tri-merisation.

Comparative data (see table) for the first main wave of certain quinoline derivatives of quinoline show that a similar mechanism to the above may apply to quinoline-2- (Stock) and -4-carboxylic acid and 8-hydroxyquinoline (Stock), but not to quinoline-8-carboxylic acid (Stock) or to quinaldine or quinoline itself (Casimir and Lyons, unpublished).

Data for the first main wave of quinoline derivatives.

Derivative :	2-CH_3.	2-CO_2H.	4-CO_2H.	8-CO_2H.	8-OH.
n.	1.	2.	2.	1.	2.
$E_{\frac{1}{2}}$ at pH 0	0·52	0·52	0·59	0·78	0·93
$E_{\frac{1}{2}}$–pH slope	0·066	0·060	0·061	0·060	0·042

It is suggested that $E_{\frac{1}{2}}$ at pH 0 values, together with *n* values, might serve to distinguish the various compounds analytically. The best conditions for straightforward polarographic analysis exist in solutions of pH < 3 where the wave is single and $E_{\frac{1}{2}}$ least negative.

Pre-steps were observed with both the waves *A* and *D* and in both cases occurred at potentials mostly independent of pH. [That to *A* occurred at 0·67 v. (pH 1·3 and 3·1); that to *D* at 1·36 v. (pH 11·8), 1·35 v. (pH 12·5), but 1·21 v. (pH 10·4).] The pre-step to *A* indicates adsorption of the ion, and that to *D* adsorption of the free base on the surface of the mercury drop (cf. Brolička, *Z. Elektrochem.*, 1942, **48**, 278), with the energy of adsorption utilised in the reduction process.

Experimental.

Buffer solutions used were made from the following solutions : pH 1·3 and 2·1 : 0·2N-KCl–0·2N-HCl; pH 3·1 and 4·0 : 0·05M-borax–0·05M-succinic acid; pH 4·9 : 0·1N-NaOH–0·1M-potassium hydrogen phthalate; pH 5·9 and 7·0 : 0·1N-NaOH–0·1M-KH_2PO_4; pH 7·2 : 0·05M-borax–0·2M-H_3BO_3; pH 8·2, 10·3, 10·6, 11·1, 11·7, and 12·4 : 0·1N-NaOH–0·1N-NaCl–0·1M-glycine; pH 8·8 and 9·0 : 0·1N-NaOH–0·1M-H_3BO_3. The cinchoninic acid (m. p. 252—253°) was prepared by H. C. Freeman, whom the authors thank. The apparatus of conventional design was manually controlled. The cell was connected by an agar-saturated potassium chloride bridge to a saturated calomel electrode, all in a thermostat keeping the temperature within ±0·01°. Purified hydrogen was used to remove dissolved oxygen. The characteristics of the capillary used for most of the work were $m = 1{\cdot}24$ mg./sec.; $t = 5{\cdot}66$ sec. (closed circuit; pH 3·08); ($m^{2/3}t^{1/6} = 1{\cdot}55$).

The 50-Ω coil resistance galvanometer was shunted and calibrated with a standard meter in series.

The University of Sydney, N.S.W., Australia. [*Received, November 17th*, 1949.]

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156. cyclo*Hexylidene Derivatives of Mannitol.*

By E. J. Bourne, W. M. Corbett, and D. Erilinne.

Concentrated acids catalyse the formation of *tricyclohexylidene mannitol* from mannitol and *cyclo*hexanone. Hydrolysis of the tricyclohexylidene compound affords a *di*- and a *mono*-cyclo*hexylidene mannitol*. Conclusive evidence is presented to show that these compounds are, respectively, the 1 : 2-3 : 4-5 : 6-, 1 : 2-3 : 4-, and 3 : 4-*cyclo*hexylidene derivatives.

As part of a wider study of the various cyclic structures which result from the condensation of hexitols with aldehydes and ketones, we have examined *tricyclohexylidene mannitol*, and have obtained unequivocal proof that the three *cyclo*hexylidene residues in this compound are attached to the 1 : 2-, 3 : 4-, and 5 : 6-positions, respectively. Thus, it is a five-membered-ring structure which is favoured in each case. We believe this to be the first occasion on which the synthesis of a *cyclo*hexylidene derivative of a hexitol has been reported.

Tri*cyclo*hexylidene mannitol was obtained as long needles when commercial D-mannitol was shaken with *cyclo*hexanone in the presence of concentrated hydrobromic or 5N-hydrochloric acid. Since dilute aqueous acid normally favours the hydrolysis of cyclic acetals, it is probable that the high proportion of the tri*cyclo*hexylidene compound present at equilibrium can be attributed to its extremely small solubility in water. When a solution of tri*cyclo*hexylidene mannitol in hot aqueous alcohol was treated with hydrochloric acid, mannitol was regenerated, an observation which clearly showed that the new compound could not have arisen from the impurities known to contaminate hexitols prepared industrially (see Bourne and Wiggins, *J.*, 1948, 1933).

Graded hydrolysis of tri*cyclo*hexylidene mannitol with aqueous hydrochloric acid in alcohol–dioxan gave a crystalline *di*- and a syrupy *mono*-cyclo*hexylidene mannitol*, together with a small amount of mannitol. The products were separated by virtue of their relative solubilities

in water, acetone, and alcohol. On appropriate treatment the mono- or the di-*cyclo*hexylidene compound regenerated the tri*cyclo*hexylidene derivative.

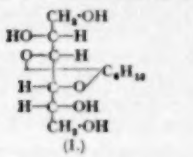
The presence of four free alcohol groups in the mono*cyclo*hexylidene mannitol was demonstrated by its conversion into three crystalline esters, namely the ***tetra-acetate***, the ***tetrabenzoate***, and the ***tetratoluene-p-sulphonate***. Catalytic deacetylation of the tetra-acetate afforded a syrup whose properties were very similar to those of the original mono*cyclo*hexylidene mannitol. This fact, together with the observation that chromatography on alumina yielded only one component, indicated that the syrupy mono*cyclo*hexylidene mannitol was not a mixture.

Proof that the *cyclo*hexylidene residue bridged positions 3 and 4 as in (I), was obtained from two different lines of approach, one involving synthesis and the other oxidative degradation. First, the well-known 1 : 2 : 5 : 6-tetrabenzoyl mannitol, prepared by Fischer (*Ber.*, 1915, **48**, 266) from 3 : 4-*iso*propylidene mannitol, was converted, by treatment with *cyclo*hexanone and hydrobromic acid, into a crystalline tetrabenzoyl mono*cyclo*hexylidene mannitol, identical with that already prepared from the syrupy mono*cyclo*hexylidene compound by benzoylation. The structures of 1 : 2 : 5 : 6-tetrabenzoyl mannitol and of the parent 3 : 4-*iso*propylidene mannitol have been well authenticated (see, *e.g.*, *Ber.*, 1932, **65**, 1055; 1933, **66**, 931, and *Helv. Chim. Acta*, 1934, **17**, 1574) and it follows that, unless acyl migration had occurred, our product was 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*cyclo*hexylidene mannitol.

Secondly, 2 atomic proportions of oxygen were taken up when mono*cyclo*hexylidene mannitol was oxidised with either lead tetra-acetate or sodium metaperiodate. The formaldehyde liberated was isolated, as its dimedone compound, in sufficient quantity to prove that two glycol groups occupied terminal positions in the mannitol molecule. Furthermore, the larger moiety resulting from the oxidation gave rise, by hydrolysis and catalytic hydrogenation, to D-threitol (II), identified as its crystalline dibenzylidene derivative. Thus the possibility of the *cyclo*hexanone residue spanning any positions other than 3 and 4 cannot be entertained.

Such a structure, possessing two unsubstituted primary alcohol groups, explains the ready formation of a dityrityl derivative (cf. Helferich, ***Advances in Carbohydrate Chem.***, 1948, Vol. **3**, p. 88). Furthermore, since the tetratoluene-*p*-sulphonate would have contiguous ester groups at positions 1 : 2 and 5 : 6, it can be seen why almost four moles of sodium toluene-*p*-sulphonate were formed when this ester was treated with sodium iodide in dry acetone (cf. Hann, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73).

Attention was now directed to the di*cyclo*hexylidene mannitol, in which two free alcohol groups were detected by the isolation of a syrupy ***diacetate*** and a syrupy ***dibenzoate***. Since the di*cyclo*hexylidene compound consumed one atomic proportion of oxygen and gave one molecular proportion of formaldehyde when treated with lead tetra-acetate or sodium metaperiodate, these hydroxy-groupings constituted a terminal α-glycol group. Consequently, the compound under examination was the 1 : 2 : 3 : 4-derivative, for the stereochemistry of mannitol obviates any necessity to distinguish between the 1 : 2- and the 5 : 6-positions. The larger fragment arising from the oxidative scission should then be a *di*cyclo***hexylidene*** aldehydo-D-***arabinose***, and a syrup which analysed correctly for this compound was in fact isolated. When hydrolysed with acid, it afforded D-arabinose, which was converted into D-arabinosazone.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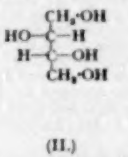
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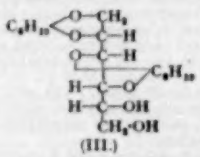
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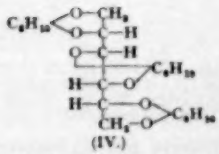
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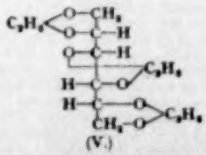
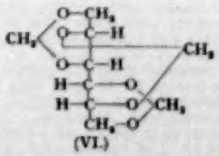

(V.)


(VI.)

Regarding the finer structure of di*cyclo*hexylidene mannitol, three possibilities remained, *viz.*: the 1 : 2-3 : 4-, the 1 : 3-2 : 4-, and the 1 : 4-2 : 3-derivative. However, graded hydrolysis

and subsequent benzoylation yielded 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*cyclo*hexylidene D-mannitol, identical with the material already prepared by two different routes, thus eliminating all but the first possibility (III). Since the mono- and di-*cyclo*hexylidene mannitols had been derived from tri*cyclo*hexylidene mannitol, the last must have been the 1 : 2-3 : 4-5 : 6-compound (IV).

The general pattern in the tri*cyclo*hexylidene mannitol molecule is thus the same as that in tri*iso*propylidene mannitol (V) (Wiggins, *J.*, 1946, 13), but different from that in trimethylene mannitol (VI) (Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 2215). In both the *cyclo*hexylidene and the *iso*propylidene series, it is the 3 : 4-derivative which is most stable under acid conditions. It is noteworthy that *cyclo*hexanone and acetone are similar also in their reactions with glucose, the 1 : 2-5 : 3-derivative being produced in each case (Hockett, Miller, and Scattergood, *J. Amer. Chem. Soc.*, 1949, **71**, 3072).

Experimental.

Attempts to purify by distillation, in a high vacuum, the syrupy *cyclo*hexylidene compounds mentioned below invariably resulted in their decomposition.

1 : 2-3 : 4-5 : 6-*Tricyclohexylidene* D-*Mannitol from Mannitol.*—Commercial mannitol (50 g.), *cyclo*hexanone (106 c.c.), and hydrobromic acid (1·25 l.; *d* 1·4) were shaken together for 20 hours and then poured into ice-water. The precipitated 1 : 2-3 : 4-5 : 6-*tricyclohexylidene* D-*mannitol* was separated by filtration, washed with dilute sodium hydroxide solution and then with water, and crystallised 3 times from alcohol in long needles (35 g.), m. p. 82·5—83·5°, $[\alpha]_D^{20}$ +15·4° (*c*, 1·24 in chloroform) [Found: C, 68·3; H, 9·25%; *M*, *ca.* 440 (Rast). $C_{21}H_{34}O_6$ requires C, 68·8; H, 9·1%; *M*, 422].

Mannitol Hexa-acetate from 1 : 2-3 : 4-5 : 6-*Tricyclohexylidene* D-*Mannitol.*—A solution of tri*cyclo*hexylidene mannitol (1·00 g.) in alcohol (30 c.c.) was heated with 2*N*-hydrochloric acid (24 c.c.) in a water-bath at 100° for 2 hours, before being diluted with water and extracted with ether to remove the *cyclo*hexanone produced. The residue obtained when the aqueous layer was evaporated at 60°/12 mm. was refluxed for 2 hours with acetic anhydride (8·0 c.c.) in the presence of fused sodium acetate (2 g.), poured into ice-water, and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and then with water, dried ($MgSO_4$), and concentrated to a syrup, which crystallised from alcohol. Recrystallised from alcohol, the product (0·45 g.) had m. p. 123°, alone or on admixture with an authentic specimen of mannitol hexa-acetate

Graded Hydrolysis of 1 : 2-3 : 4-5 : 6-*Tricyclohexylidene* D-*Mannitol.*—A suspension of tri*cyclo*hexylidene mannitol (45 g.) in a mixture of dioxan (230 c.c.), alcohol (100 c.c.), and 5*N*-hydrochloric acid (70 c.c.) was kept at 35°, with occasional shaking, for 2 hours, by which time dissolution was complete. The solution was neutralised with lead carbonate, and the lead salts were removed by filtration before being washed with a little water and then with acetone. The filtrate and washings were combined and concentrated at 40°/12 mm. to a syrup, which was extracted several times with water. Trituration of the insoluble residue with acetone afforded tri*cyclo*hexylidene mannitol as needles (9·84 g.), m. p. and mixed m. p. 82·5°. The acetone-soluble fraction was crystallised once from aqueous alcohol and twice from light petroleum, giving 1 : 2-3 : 4-*dicyclohexylidene* D-*mannitol* (8·62 g.), m. p. 52—54°, $[\alpha]_D^{20}$ +11·2° (*c*, 1·97 in chloroform) (Found: C, 63·1; H, 9·0. $C_{15}H_{26}O_6$ requires C, 63·1; H, 8·8%).

The combined aqueous extracts were concentrated to a clear syrup, which deposited crystals of mannitol (4·0 g.) (confirmed by acetylation) from absolute alcohol. Evaporation of the alcoholic mother-liquors left 3 : 4-cyclo*hexylidene* D-*mannitol* (10·0 g.) as a syrup which, when dried at 65°/0·05 mm. for 1 hour, had n_D^{20} 1·4925, $[\alpha]_D^{20}$ +17·4° (*c*, 1·99 in chloroform) (Found: C, 55·0; H, 8·4. $C_{12}H_{22}O_6$ requires C, 54·9; H, 8·5%).

1 : 2-3 : 4-5 : 6-*Tricyclohexylidene* D-*Mannitol from* 1 : 2-3 : 4-*Dicyclohexylidene* D-*Mannitol.*—Di*cyclo*hexylidene mannitol (0·04 g.), *cyclo*hexanone (0·20 c.c.), and 5*N*-hydrochloric acid (3·0 c.c.) were shaken together for 30 minutes and the solid product was removed by filtration. After being washed with water, it recrystallised from aqueous alcohol in needles, m. p. 80—82°, alone or on admixture with 1 : 2-3 : 4-5 : 6-tri*cyclo*hexylidene mannitol prepared directly from mannitol.

1 : 2-3 : 4-5 : 6-*Tricyclohexylidene* D-*Mannitol from* 3 : 4-cyclo*Hexylidene* D-*Mannitol.*—3 : 4-*cyclo*Hexylidene mannitol (0·50 g.), *cyclo*hexanone (0·70 c.c.), and 5*N*-hydrochloric acid (4·0 c.c.) were shaken together for 20 hours. The solid product was removed by filtration, washed with sodium hydrogen carbonate solution and then with water, and crystallised from aqueous alcohol in needles (0·39 g.), m. p. 82—83°, alone or on admixture with 1 : 2-3 : 4-5 : 6-tri*cyclo*hexylidene mannitol prepared directly from mannitol.

1 : 2 : 5 : 6-*Tetra-acetyl* 3 : 4-cyclo*Hexylidene* D-*Mannitol.*—3 : 4-*cyclo*Hexylidene mannitol (3·06 g.) was treated with pyridine (12·0 c.c.)–acetic anhydride (6·0 c.c.) for 48 hours at 18°. The oil which separated when the solution was poured into ice-water crystallised after several hours. Recrystallised 3 times from aqueous alcohol, the *acetate* (3·07 g.) had m. p. 67—68·5°, $[\alpha]_D^{20}$ +50·7° (*c*, 1·12 in chloroform) (Found: C, 55·5; H, 7·0; Ac, 39·1. $C_{20}H_{30}O_{10}$ requires C, 55·8; H, 7·0; Ac, 40·0%).

Regeneration of 3 : 4-cyclo*Hexylidene* D-*Mannitol from its Tetra-acetate.*—The tetra-acetate (0·552 g.) was treated for 48 hours with a trace of sodium in absolute methanol (10 c.c.). Carbon dioxide was bubbled through the solution, and the solvent was removed by distillation. The dry residue was extracted with chloroform. Concentration of the extracts afforded 3 : 4-*cyclo*hexylidene D-mannitol as a syrup (0·286 g.), n_D^{20} 1·4965, $[\alpha]_D^{20}$ +17·7° (*c*, 1·18 in chloroform).

1 : 2 : 5 : 6-*Tetrabenzoyl* 3 : 4-cyclo*Hexylidene* D-*Mannitol.*—Benzoyl chloride (1·50 c.c.) was added to a cooled solution of 3 : 4-*cyclo*hexylidene mannitol (0·659 g.) in pyridine (3·0 c.c.). After 18 hours at room temperature, the solution was poured into water and the precipitate collected. Three crystallisations from acetone–alcohol gave 1 : 2 : 5 : 6-*tetrabenzoyl* 3 : 4-cyclo*hexylidene* D-*mannitol*

(0·806 g.), m. p. 147·5—148·5°, $[\alpha]_D^{20}$ −7·7° (*c*, 1·16 in chloroform) (Found: C, 71·0; H, 5·8. $C_{26}H_{34}O_{10}$ requires C, 70·8; H, 5·65%).

1 : 2 : 5 : 6-*Tetratoluene-p-sulphonyl* 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—3 : 4-*cyclo*Hexylidene mannitol (0·829 g.) was treated with toluene-*p*-sulphonyl chloride (2·66 g.) in pyridine (10 c.c.) at 35° for 72 hours, before being poured into ice-water and extracted with chloroform. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and water, dried ($MgSO_4$), filtered, and concentrated to a syrup, which crystallised from absolute alcohol. After 3 more crystallisations, the *product* (0·385 g.) had m. p. 135—137°, $[\alpha]_D^{20}$ +4·9° (*c*, 1·03 in chloroform) (Found: C, 54·9; H, 5·4; S, 14·0. $C_{68}H_{74}O_{18}S_4$ requires C, 54·7; H, 5·3; S, 14·6%).

Reaction of 1 : 2 : 5 : 6-*Tetratoluene-p-sulphonyl* 3 : 4-cyclo*Hexylidene* D-*Mannitol with Sodium Iodide in Acetone*.—The toluene-*p*-sulphonate (0·1007 g.) and sodium iodide (0·204 g.) were dissolved in dry acetone (15 c.c.) and heated in a sealed tube at 100—110° for 8 hours. The precipitated sodium toluene-*p*-sulphonate (0·0833 g.) represented an exchange of 3·75 ester groups per molecule.

1 : 6-*Ditrityl* 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—3 : 4-*cyclo*Hexylidene mannitol (0·350 g.) and triphenylmethyl chloride (0·745 g.) were dissolved in pyridine (3·0 c.c.) and kept at room temperature for 48 hours. The sticky solid ether (0·950 g.), which separated when the solution was poured into ice-water, could not be crystallised. It had $[\alpha]_D^{20}$ +12·5° (*c*, 1·12 in chloroform).

2 : 5-*Diacetyl* 1 : 6-*Ditrityl* 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—1 : 6-Ditrityl 3 : 4-*cyclo*hexylidene mannitol (0·706 g.) was dissolved in pyridine (2·0 c.c.) and acetic anhydride (0·5 c.c.) was added. After 18 hours, the mixture was poured into ice-water and extracted with chloroform. The extracts were washed with dilute acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), filtered, and evaporated. The residual solid, crystallised 3 times from acetone–alcohol–water, afforded 2 : 5-*diacetyl* 1 : 6-*ditrityl* 3 : 4-cyclo*hexylidene* D-*mannitol* (0·532 g.), m. p. 197—198°, $[\alpha]_D^{20}$ ±0·0° (*c*, 0·93 in chloroform) (Found: C, 78·0; H, 6·6. $C_{64}H_{58}O_8$ requires C, 78·0; H, 6·6%).

1 : 2 : 5 : 6-*Tetrabenzoyl* D-*Mannitol*.—Hydrolysis of 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*iso*propylidene D-mannitol (0·503 g.; m. p. 121°) by the method of Fischer (*loc. cit.*) gave 1 : 2 : 5 : 6-tetrabenzoyl D-mannitol (0·387 g.), m. p. 117—119°, $[\alpha]_D^{20}$ +7·9° (*c*, 1·3 in tetrachloroethane) (Found: C, 68·3; H, 5·2. Calc. for $C_{34}H_{30}O_{10}$: C, 68·2; H, 5·1%). Fischer (*loc. cit.*) gave m. p. 122—123°, $[\alpha]_D^{20}$ +7·83° in tetrachloroethane.

Treatment of 1 : 2 : 5 : 6-*Tetrabenzoyl* D-*Mannitol with* cyclo*Hexanone*.—The tetrabenzoate (0·050 g.), *cyclo*hexanone (2·0 c.c.), and hydrobromic acid (0·5 c.c.; *d* 1·4) were shaken together for 18 hours. The heavy oil, which separated when the reaction mixture was poured into ice-water, crystallised when triturated with alcohol. Recrystallisation from acetone–alcohol gave 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*cyclo*hexylidene D-mannitol (0·049 g.), m. p. 147·5—148·5° (alone or on admixture with the compound mentioned above), $[\alpha]_D^{20}$ −7·7° (*c*, 0·65 in chloroform).

Lead Tetra-acetate Oxidation of 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—Tetra-acetyl *cyclo*hexylidene mannitol ($3·93 \times 10^{-4}$ mole) was deacetylated with sodium in methanol, and the product was oxidised with lead tetra-acetate according to the procedure of Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667). The number of g.-atoms of oxygen taken up per g.-mol. was 0·37 (10 minutes), 1·26 (60 minutes), 1·64 (120 minutes), 1·84 (180 minutes), and 1·98 (300 minutes).

Periodate Oxidation of 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—(a) *Isolation of formaldehyde*. 3 : 4-*cyclo*Hexylidene mannitol ($0·4 \times 10^{-4}$ moles) was oxidised under the conditions recommended by Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476), and, in 4 hours, $0·673 \times 10^{-4}$ mole of formaldehyde, isolated as its dimedone derivative (m. p. 189°), was liberated. This represented 1·68 moles of formaldehyde per mole of *cyclo*hexylidene mannitol. Longer periods of oxidation resulted in somewhat lower yields of formaldehyde, presumably because this initial product was slowly oxidised to formic acid (cf. Hirst and Jones, *J.*, 1949, 1659).

(b) *Isolation of dibenzylidene* D-*threitol*. 3 : 4-*cyclo*Hexylidene mannitol (3·310 g.) was dissolved in the minimum volume of water and an aqueous solution (50 c.c.) of sodium metaperiodate (5·12 g.) was added. After 24 hours at room temperature, the solution was saturated with salt and extracted with chloroform. The extract was dried ($MgSO_4$), filtered, and concentrated to a syrup (0·847 g.) which showed positive Schiff's and Fehling's tests and had n_D^{15} 1·4845, $[\alpha]_D^{20}$ (equilibrium) −23·1° (*c*, 1·17 in chloroform). This probably was 2 : 3-*cyclo*hexylidene D-*threo*dihydroxysuccinic dialdehyde.

The syrup (0·574 g.) was hydrolysed with *N*-sulphuric acid (12·5 c.c.) at 100° for 3 hours. The solution was neutralised with barium carbonate, filtered, and evaporated at 35°/12 mm. The residue was extracted with absolute methanol, and evaporation of the solution left a resinous residue (0·173 g.), which rapidly reduced Fehling's solution.

The D-*threo*dihydroxysuccinic dialdehyde was hydrogenated with Raney nickel in alcohol (50 c.c.) at 40°/30 atm. for 20 hours. The catalyst was removed by filtration and the filtrate was concentrated to a syrup, which was dissolved in absolute methanol (25 c.c.). The solution was saturated with dry hydrogen chloride, benzaldehyde (10 c.c.) was added, and the mixture was shaken for 20 hours, before being neutralised with sodium hydrogen carbonate and filtered. The filtrate was evaporated at 40°/12 mm. and the solid residue was extracted with chloroform. Removal of the solvent left a solid, which afforded dibenzylidene D-threitol (0·050 g.), m. p. 227°, $[\alpha]_D^{20}$ −94·5° (*c*, 0·275 in pyridine), when crystallised twice from alcohol and once from dioxan. Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1943, **65**, 1663) give m. p. 231°, $[\alpha]_D^{20}$ −90·2° (*c*, 0·80 in pyridine), for dibenzylidene D-threitol.

5 : 6-*Diacetyl* 1 : 2-3 : 4-*Dicyclohexylidene* D-*Mannitol*.—*Dicyclo*hexylidene mannitol (0·508 g.) was acetylated with acetic anhydride (1·10 c.c.) in pyridine (2·50 c.c.). After 20 hours, the solution was poured into ice-water and extracted with chloroform. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), filtered, and concentrated to a clear syrup, from which the last traces of solvent were removed at 65°/0·1 mm. The *product* (0·464 g.) had n_D^{15} 1·4798, $[\alpha]_D^{20}$ +24·9° (*c*, 1·33 in chloroform) (Found: C, 61·9; H, 8·3; Ac, 19·4. $C_{28}H_{44}O_8$ requires C, 61·9; H, 8·0; Ac, 20·2%).

5 : 6-*Dibenzoyl* 1 : 2-3 : 4-*Dicyclohexylidene* D-*Mannitol*.—*Dicyclo*hexylidene mannitol (0·219 g.) was treated for 18 hours with benzoyl chloride (0·76 c.c.) in pyridine (1·5 c.c.) and then poured into ice-water.

The aqueous solution was extracted with chloroform. The extract was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. It was dried (Na_2SO_4), filtered, and evaporated to a syrup, from which all residual solvent was removed at 60°/0·05 mm. during 1 hour. The *product* (0·146 g.) showed $[\alpha]_D^{15}$ +7·4° (*c*, 1·1 in chloroform) and n_D^{15} 1·5475 (Found: C, 69·7; H, 6·9. $C_{18}H_{34}O_9$ requires C, 69·5; H, 7·0%).

Lead Tetra-acetate Oxidation of 1 : 2-3 : 4-*Dicyclohexylidene* D-*Mannitol*.—When dicyclohexylidene mannitol ($4·83 \times 10^{-4}$ moles) was oxidised with lead tetra-acetate, according to the method of Hockett and McClenahan (*loc. cit.*), the number of g.-atoms of oxygen taken up per g.-mol. was 0·46 (30 minutes), 0·56 (80 minutes), 0·78 (140 minutes), 0·88 (210 minutes), 0·95 (260 minutes), and 1·02 (320 minutes).

Periodate Oxidation of 1 : 2-3 : 4-*Dicyclohexylidene* D-*Mannitol*.—(a) *Isolation of formaldehyde.* Dicyclohexylidene mannitol, oxidised for 4 hours under the conditions recommended by Reeves (*loc. cit.*), gave, per mole, 1·04 moles of formaldehyde, isolated as its dimedone derivative (m. p. 189°).

(b) *Isolation of* 2 : 3-4 : 5-*dicyclohexylidene* aldehydo-D-*arabinose*. Dicyclohexylidene mannitol (1·00 g.) was dissolved in alcohol (3·0 c.c.), and water was added until there was a slight turbidity. Potassium metaperiodate (1·345 g.) was introduced and the mixture was shaken for 18 hours, before being saturated with sodium chloride and extracted with chloroform. The extract was dried (Na_2SO_4), filtered, and concentrated to a syrup, from which all the residual solvent was removed at 35°/0·005 mm. The *product* (0·78 g.), which restored the colour to decolorised magenta, had n_D^{15} 1·4890, $[\alpha]_D^{15}$ −5·3° (*c*, 0·94 in chloroform) (Found: C, 65·5; H, 8·6. $C_{11}H_{18}O_5$ requires C, 65·7; H, 8·4%).

(c) *Isolation of* D-*arabinose*. A portion of the dicyclohexylidene *aldehydo*-D-arabinose (0·392 g.) was hydrolysed with N-sulphuric acid (7·5 c.c.) at 100° for 2 hours. The solution was neutralised with barium carbonate and filtered, and the filtrate concentrated at 35°, leaving a white solid. This was extracted with absolute methanol, from which crystals were deposited when the volume was reduced. Recrystallised from absolute methanol, the product (0·150 g.) had m. p. 158—159°, alone or on admixture with D-arabinose, $[\alpha]_D^{15}$ (equilibrium) −101·5° (*c*, 0·61 in water), compared with accepted values m. p. 159—160°, $[\alpha]_D^{20}$ (equilibrium) −104·5° (in water). With phenylhydrazine, under the usual conditions, it yielded D-arabinosazone, m. p. 162—163°.

3 : 4-cyclo*Hexylidene* D-*Mannitol from* 1 : 2-3 : 4-*Dicyclohexylidene* D-*Mannitol*.—Dicyclohexylidene D-mannitol (1·08 g.) was dissolved in alcohol (80 c.c.), and concentrated hydrochloric acid (20 c.c.) was added. After 150 minutes, the solution was neutralised with lead carbonate. The lead salts were removed by filtration and washed, first with a little water and then with acetone. The combined filtrate and washings were concentrated, the residue being extracted with water. The aqueous solution was evaporated, leaving a syrup, from which a little mannitol crystallised on trituration with acetone. Concentration of the acetone solution yielded a syrup, which was treated for 48 hours with benzoyl chloride (0·75 c.c.) in pyridine (1·50 c.c.). The product was precipitated with alcohol. Recrystallisation from acetone–alcohol gave 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*cyclo*hexylidene D-mannitol (0·443 g.), m. p. 147·5—148·5°, alone or on admixture with either of the compounds mentioned above.

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THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, December 7th*, 1949.]

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157. *The Manganohalides of Pyridine.*

By W. S. FYFE.

Dipyridinomanganous chloride combines with dry hydrogen chloride to form a green compound, previously formulated as $(PyH)_2MnCl_4$ and here reformulated as $H_2MnPy_2Cl_4$. The double salt $MnCl_2.PyHCl.H_2O$ has also been reformulated as the acid $H_2MnPyCl_3(OH)$. The potassium salts of these acids have been isolated.

A NUMBER of compounds of pyridine and manganous chloride have been described previously. Pincussohn (*Z. anorg. Chem.*, 1897, **14**, 388) gave details of a yellow compound, $MnCl_2.2PyHCl$, and a pink compound, $MnCl_2.PyHCl$, whilst Reitzenstein (*ibid.*, 1898, **18**, 290) described a green compound, $MnPy_2Cl_4$, and a pink salt, $MnPy_4Cl_2$. Meyer and Best (*ibid.*, 1900, **22**, 182) described the bromide, $MnBr_2.2PyHBr$. Taylor (*J.*, 1934, 699) revised this work and came to the following conclusions: (*a*) Pincussohn's yellow compound and Reitzenstein's green compound were identical and best formulated as $(PyH)_2MnCl_4$; (*b*) Pincussohn's pink compound was $MnCl_2.PyHCl.H_2O$; (*c*) Reitzenstein had reported that when the green compound, $MnPy_2Cl_4$, was pressed between filter papers the pink compound, $MnPy_4Cl_2$, was produced, chlorine being evolved in the change. Taylor proved that no loss of chlorine occurred and that the product was $MnCl_2.PyHCl.H_2O$; (*d*) the green colour of concentrated solutions was due to the $MnCl_4^{--}$ ion and the pink colour of more dilute solutions was due to the $(MnCl_2.H_2O)^{--}$ ion.

The present investigation indicates that, in the case of the green complex, the pyridine is bound to the manganese atom and is not present as the pyridinium ion. This compound has been reformulated as the complex dibasic acid, $H_2MnPy_2Cl_4$. The

compound, $MnCl_2.PyHCl.H_2O$, described by Taylor, has also been reformulated as the acid, $H_2MnPyCl_3(OH)$. The identity of the pink salt, $MnPy_2Cl_2$, described by Reitzenstein has been confirmed, and a new salt, $MnPy_4Cl_2.2H_2O$, described.

Experimental.

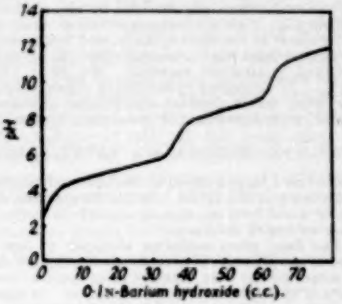
Dipyridinomanganous Chloride.—This compound is precipitated as fine pink needles on addition of pyridine to alcoholic solutions of manganous chloride. These can be washed in ether, vacuum dried, and recrystallised from alcohol (Found: Mn, 19·1; Cl, 25·2; N, 8·3. Calc. for $MnPy_2Cl_2$: Mn, 19·4; Cl, 25·0; N, 9·9%). Addition of pyridine to concentrated aqueous solutions of manganous chloride also precipitates this compound, which is also obtained when pyridine is added to a hot solution of manganous chloride in concentrated hydrochloric acid, but it then redissolves to form the green complex, $H_2MnPy_2Cl_4$.

All the chloride ions are precipitated in the cold by silver nitrate. The molar conductivities measured at 25° were:

Molar concentration	0·1	0·01	0·005	0·0025	0·0012
Conductivity (mhos)	164	191	216	250	280

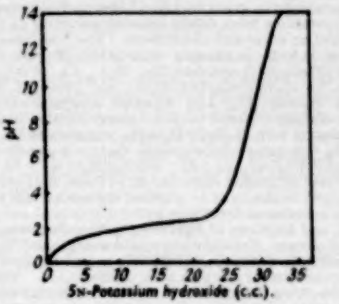
These measurements are in harmony with complete ionisation into $MnPy_2^{++}$ and $2Cl^-$. Freezing-point depressions in water gave a value of 68 for the molecular weight (Calc. for $MnPy_2Cl_2$: 284), *i.e.*, a van't Hoff's factor (*i*) of 4·2, indicating that the complex ion, $MnPy_2^{++}$, is also partly dissociated.

Fig. 1.



Neutralisation curve of 20 *c.c. of* 0·1M-$H_2MnPy_2Cl_4$.

Fig. 2.



Neutralisation curve of 15 *c.c. of* 5M-$H_2MnPy_2Cl_4$.

Dipyridinomanganous Chloride Dihydrate.—This compound crystallises in large white crystals from dilute solutions of manganous chloride and pyridine, and was originally found in the residues remaining after the crystallisation of $MnPy_2Cl_2$ (Found: Mn, 16·9; Cl, 22·1. $MnPy_2Cl_2.2H_2O$ requires Mn, 17·2; Cl, 22·2%). The *dihydrate* loses the two molecules of water on continued vacuum desiccation. It is not deliquescent but is readily soluble in water. Freezing-point and conductivity data are identical with those obtained for $MnPy_2Cl_2$, indicating that in solution the states of dipyridinomanganous chloride and its dihydrate are probably identical.

Hydrogen Tetrachlorodipyridinomanganate(II).—(*a*) This compound was prepared by Reitzenstein's method of adding pyridine to a solution of manganese dioxide in hydrochloric acid. On evaporation to dryness on a water-bath the green compound was obtained.

(*b*) The compound was similarly prepared from manganic oxide and trimanganese tetroxide.

(*c*) It can also be prepared by evaporating to dryness a solution of manganous chloride in hydrochloric acid and pyridine. Pale green crystals are obtained, and this material was used in physical measurements.

(*d*) The green material was also prepared by passing dry hydrogen chloride over dipyridinomanganous chloride, this change occurring very rapidly; the dihydrate does not change under these conditions.

Examination of the compounds, prepared in these different ways, by both analytical and optical methods indicated their identity (Found: Mn, 15·3; Cl, 39·6; N, 7·2. Calc. for $H_2MnPy_2Cl_4$: Mn, 15·4; Cl, 39·7; N, 7·8%). The apparent optic axial angle is $59° \pm 2°$; n_B 1·653 ± 0·002.

The material was purified by boiling in ether and chloroform, to remove traces of hydrogen chloride and pyridine hydrochloride. Recrystallisation from alcohol and water is not possible, and recrystallisation from pyridine produces dipyridinomanganous chloride, a change which gives some indication of the strength with which the hydrogen chloride is held in the lattice. The material was dried at about 1 mm.

A typical neutralisation curve for the complex is given in Fig. 1. In dilute solution a two-stage curve is obtained, the first stage corresponding to the neutralisation of the pyridinium ion and the

second to the precipitation of manganous hydroxide. However, in concentrated solutions a one-stage curve, corresponding to the neutralisation of the acid, $H_2MnPy_2Cl_4$, is given (Fig. 2). In dilute solutions this material is extensively hydrolysed. Freezing-point depressions in aqueous solutions gave a value of 80 for the molecular weight (Calc. for $H_2MnPy_2Cl_4$: 357). This gives a value for i of 4·4. Molar conductivities measured at 20° were:

Molar concentration	5	0·5	0·1	0·01	0·001
Conductivity (mhos)	7	117	186	220	260

Preparation of $H_2MnPy_2Cl_4$ from Manganese Dioxide and Manganous Chloride.—Manganese dioxide dissolved in hydrochloric acid, in the presence of pyridine at 0°, formed at first a deep green solution and only slight amounts of chlorine were evolved even on warming the solution on a water-bath. It thus appeared that the deep green solution contained a complex ion of quadrivalent manganese. When the solution was evaporated to crystallisation little chlorine was evolved until near the crystallisation point when chlorine was liberated quantitatively: $MnO_2 + 4HCl = MnCl_2 + Cl_2 + 2H_2O$. At this stage the solution became a pale green and pale green crystals separated. The preparation of the green complex from manganous chloride was also studied, and no oxygen absorption, as occurs in the oxidation of the cobaltous amines, or hydrogen evolution was observed. It thus appears that the complex could not be other than one of the manganous ion.

Potassium Tetrachlorodipyridinomanganate(II).—This pink *salt* was precipitated when a green, concentrated solution of the acid was neutralised with concentrated potassium hydroxide. It is fairly soluble in water. If dilute solutions of the acid are used manganous hydroxide is precipitated (Found: Mn, 12·4; Cl, 33·0; Py, 38·0; K, 16·2. $K_2MnPy_2Cl_4$ requires Mn, 12·6; Cl, 32·8; Py, 36·6; K, 18·0%). The isolation of this material indicates that the green complex contains the $MnPy_2Cl_4^{--}$ ion.

Hydrogen Trichlorohydrosopyridinomanganate(II).—This compound was prepared by Reitzenstein by pressing the green complex between filter papers, and was erroneously recorded by him as $MnPy_2Cl_3$. It crystallises from dilute aqueous solutions of $H_2MnPy_2Cl_4$; pink crystals are obtained which can be washed in ether and chloroform. The *compound* crystallises as the monohydrate, and this molecule of water is lost on vacuum desiccation (Found, in vacuum-desiccated material: Mn, 21·1; Cl, 41·0. $H_2MnPyCl_3(OH)$ requires Mn, 21·1; Cl, 41·0%. Found in air-dried material: Mn, 19·5; Cl, 38·4. Calc. for $H_2MnPyCl_3(OH).H_2O$: Mn, 19·9; Cl, 38·6%). It undergoes hydrolysis in dilute solutions as does $H_2MnPy_2Cl_4$, and repeated recrystallisations from water produce manganous chloride. By neutralising concentrated solutions of the pink acid with concentrated potassium hydroxide the potassium salt, $K_2MnPyCl_3(OH)$, was obtained.

In this series of compounds there is a steady drop in the β refractive index: $H_2MnPy_2Cl_4$, n_β 1·653; $H_2MnPyCl_3(OH)$, n_β 1·62; $MnCl_2.2H_2O$, n_β 1·59.

Ionic Migration Experiments.—These were conducted on a large number of the coloured solutions to obtained evidence as to whether the colour was in the anion or the cation. In the deep green solution from manganese dioxide in hydrochloric acid and pyridine and from manganous chloride in hydrochloric acid, and solutions of $H_2MnPy_2Cl_4$ the colour was associated with the anion.

Hydrogen Hexachlorodipyridinomanganate(IV).—The deep green solutions obtained at first from the solution of manganese dioxide in hydrochloric acid in the presence of pyridine most probably contain the quadrivalent complex acid, $H_2MnPy_2Cl_6$. This compound has been obtained in an impure condition by dissolving manganese dioxide in an ethereal solution of hydrogen chloride and pyridine. It separates as a green viscous liquid. All attempts to crystallise the material have led to its decomposition, and the formation of $H_2MnPy_2Cl_4$.

Nitrogen could not be determined satisfactorily by the Kjeldahl method; the method used was to steam-distil the pyridine from a strongly alkaline solution of the complex, and titrate the pyridine with hydrochloric acid, using a pH-meter.

Discussion.

There is no doubt that Reitzenstein's formulation of the green complex as $MnPy_2Cl_4$ is incorrect; the compound does not contain quadrivalent manganese. Taylor formulated this complex as a pyridinium salt and doubtless much of the evidence from dilute solutions supports this view as the pyridinium ion is a product of the hydrolysis of the $MnPy_2Cl_4^{--}$ ion. However, the isolation of the alkali-metal salts supports the formulation of the green complex as the acid, $H_2MnPy_2Cl_4$. The very rapid entry of hydrogen chloride into the complex $MnPy_2Cl_2$ to form $H_2MnPy_2Cl_4$ when the gas is passed over the material, and its equally ready removal by washing it with pyridine, suggests that the hydrogen chloride molecule is co-ordinated and not taking part in the formation of a pyridinium ion. The addition of hydrogen chloride resembles the change of $PtCl_4$ to H_2PtCl_6 in which two molecules of hydrogen chloride are co-ordinately bound. This compound also is hydrolysed in water, losing hydrochloric acid. The complex dipyridinomanganous chloride contains two molecules of pyridine co-ordinated by the lone pair on the nitrogen to the manganese. The formation of the pyridinium salt $(PyH)_2MnCl_4$ by molecular rearrangement on exposure of the salt to hydrogen chloride would be improbable. Moreover, the hydrogen chloride is easily removed by treating the compound with pyridine. It is more probable that the chlorine atoms on the hydrogen chloride molecules fill up the remaining spaces in the lattice, donating their lone pairs and giving the manganous ion six-fold co-ordination. Freezing-point depressions do not support the presence of a three-ion salt and the stability in Kjeldahl nitrogen determinations is not to be expected from a pyridinium salt.

Two different structures have been proposed for dipyridinomanganous chloride; Cox, Shorter, Wardlaw, and Way (*J.*, 1937, 1556) concluded that the structure was similar to that of dipyridinocobaltous chloride, which has a *trans*-planar configuration. Mellor and Coryell (*J. Amer. Chem. Soc.*, 1938, **60**, 1786) proposed an octahedral configuration from magnetic evidence. As the maximum co-ordination number of the manganous ion is six, it is not obvious, on the latter hypothesis, how water and hydrogen chloride could enter the lattice to give $MnPy_2Cl_2.2H_2O$ and $H_2MnPy_2Cl_4$.

Assuming the planar configuration, however, this addition could readily occur with the production of an octahedral configuration. It is noteworthy that hydrogen chloride has no effect on $MnPy_2Cl_2.2H_2O$, probably because there are no positions of entry for this molecule.

The instability of the green liquid, $H_2MnPy_2Cl_4$, is not unexpected on structural grounds, for in this compound the small quadrivalent manganese ion is in eight co-ordination.

Some evidence of the hydrolysis of the green acid in dilute solutions comes from the formation of the compounds $H_2MnPyCl_3(OH)$ and eventually $MnCl_2.2H_2O$ on continued recrystallisation. The change is essentially H–OH for H–Cl as occurs in the case of the platinic acids. As the complex ion is considerably dissociated the hydrogen chloride liberated will combine with any free pyridine from the dissociation $MnPy_2Cl_4^{--} \rightleftharpoons MnCl_4^{--} + 2Py$. The position of the pyridine molecule will then be taken by a water molecule. This change evidently at first goes only one stage, for $H_2MnPyCl_3(OH)$ can be isolated. A general scheme for the hydrolysis is:

$$H_2MnPy_2Cl_4 + 2HOH \longrightarrow H_2MnPyCl_3(OH).H_2O + PyHCl$$
$$H_2MnPyCl_3(OH).H_2O + 2H_2O \longrightarrow MnCl_2.4H_2O + PyHCl$$

The hydrolysis products and not the parent ions account for the properties of the dilute solutions. The freezing-point depressions indicate that in all cases the complex ions are considerably dissociated. Again the precipitation of the manganese ion by phosphate indicates that a considerable amount of the ion is present at equilibrium. The chloride ions are also readily precipitated from all the complexes. Magnetic measurements (Selwood, "Magnetochemistry," p. 153, Interscience Publishers, N.Y., 1943) show that all the complexes are paramagnetic and that no coupling of electrons has occurred; they are thus *normal* complexes on the Biltz classification. This is in agreement with their instability.

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UNIVERSITY OF OTAGO, DUNEDIN, NEW ZEALAND. [*Received, August 15th*, 1949.]

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158. *Studies in Molecular Rearrangement. Part II.* Oxotropic Rearrangements in the Polycyclic Aromatic Series.*

By E. A. BRAUDE, J. S. FAWCETT, and D. D. E. NEWMAN.

The 1-aryl-3-methylallyl alcohols (I), where X = 1-naphthyl, 2-naphthyl, 9-anthryl, and 9-phenanthryl, have been prepared. They readily undergo the expected oxotropic rearrangements in the presence of dilute acids to give the corresponding 3-aryl-1-methylallyl alcohols (II). The structure of the latter was proved by Oppenauer oxidation to the ketones (III)

X·CH(OH)·CH:CHMe (I.) ⟶ X·CH:CH·CH(OH)Me (II.) ⟶ X·CH:CH·COMe (III.)

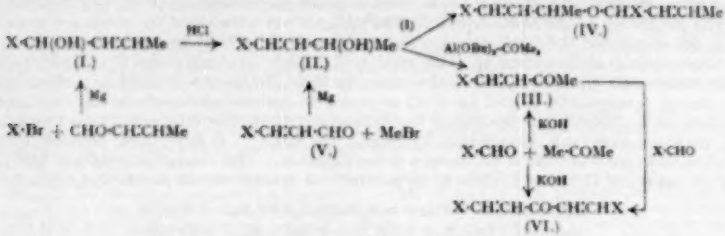
which were also obtained by condensation of the appropriate aryl aldehydes with acetone. The various derivatives have been characterised by their ultra-violet light-absorption properties which exhibit a number of interesting features.

In two earlier papers (Braude, Jones, and Stern, *J.*, 1946, 396; 1947, 1087) the oxotropic rearrangements of phenylpropenylcarbinol (I; X = Ph) and of a number of nuclear-substituted phenylpropenylcarbinols (I; X = C_6H_4R) to the corresponding styrylmethylcarbinols (II) have been described. The rearrangements take place very readily in the presence of dilute acids, and at room temperature proceed either to completion or to equilibrium mixtures containing more than 90% of the conjugated isomers (II), as would be expected since the latter are stabilised by the considerable additional resonance energy of the styryl or substituted styryl system (Braude and Stern, *J.*, 1947, 1096). It was of interest to extend the range of this reaction to polycyclic aromatic derivatives in order to obtain some evidence concerning the conjugating properties of polycyclic aromatic groups. Moreover, a kinetic study

* A paper by Braude, Jones, and Stern, *J.*, 1947, 1087, is regarded as Part I.

of such rearrangements and a comparison with the data for phenylpropenylcarbinol would provide some quantitative information, which has been almost entirely lacking hitherto, regarding the effects of polycyclic aryl groups on reactivity.

The four *arylpropenylcarbinols* (*1-aryl-3-methylallyl alcohols*) (I), where X = 1-naphthyl, 2-naphthyl, 9-anthryl, and 9-phenanthryl, were prepared by the Grignard condensation of the appropriate aryl bromides with crotonaldehyde. After careful purification by fractionation in high vacuum or chromatography, the carbinols were obtained as low-melting crystalline solids, with the exception of the 1-naphthyl derivative which is a viscous liquid at room temperature.



On treatment with dilute hydrochloric acid in aqueous acetone at room temperature, the arylpropenylcarbinols were readily converted into the higher-melting *methyl-2-arylvinylcarbinols* (*3-aryl-1-methylallyl alcohols*) (II), which were also characterised by their *p-nitrobenzoates*. The isomerisations takes place practically quantitatively under suitable conditions and in sufficiently dilute solution. At high carbinol concentrations some self-etherification may occur; thus, a 7% solution of 1-naphthylpropenylcarbinol in 90% aqueous acetone–0·1M-hydrochloric acid afforded the rearranged carbinol in only 30% yield, together with a 55% yield of a higher-boiling product, which from its analytical data, its light absorption properties, and the absence of " active " hydrogen, must be formulated as the " half-rearranged " *ether* (IV) derived from one molecule of unrearranged, and one molecule of rearranged carbinol. On carrying out the rearrangement with a more dilute, 2·5%, solution of the carbinol in 60% aqueous acetone under otherwise identical conditions, the rearranged carbinol is obtained in 90% yield, and hardly any of the ether is formed. Self-etherification in the course of oxotropic rearrangement has previously been observed with ethynylpropenylcarbinol (I; X = CH:C) (Heilbron, Jones, and Weedon, *J.*, **1945**, **81**), but in this case the resulting ether was fully rearranged. These reactions are analogous to the easy cross-etherification of propenylcarbinols with methanol or ethanol which have also been shown to occur both with and without rearrangement in aqueous-alcoholic solution in the presence of dilute acids (Heilbron, Jones, and Weedon, *loc. cit.*; Braude, Jones, and Stern, *loc. cit.*; Braude and Stern, *loc. cit.*).

Although the 3-aryl-1-methylallyl alcohols (II) differ from the 1-aryl-3-methylallyl alcohols in their ultra-violet light-absorption properties, the spectral data do not in every case provide conclusive evidence for the structure of the rearranged carbinols (see below). The structures of the latter were unambiguously proved, however, by Oppenauer oxidation to the methyl 2-arylvinyl ketones (III) which were obtained in good yields. The ketones were synthesised independently by condensation of the appropriate aryl aldehydes with acetone and characterised by their 2 : 4-*dinitrophenylhydrazones*. The preparation of methyl 2-1′- and methyl 2-2′-naphthylvinyl ketone has been previously described (Gibson, Hariharan, Menon, and Simonsen, *J.*, **1926**, **2247**; Wilds, Beck, Close, Djarassi, Johnson, Johnson, and Shunk, *J. Amer. Chem. Soc.*, **1947**, **69**, **1985**). The reaction between 9-anthraldehyde and acetone in acid or alkaline solution was found to give largely the high-melting di-condensation product *di-(2-9′-anthrylvinyl) ketone* (VI; X = 9-anthryl) unless a large excess of acetone was employed. As might be expected in view of this result, the mono-condensation product, *methyl 2-9′-anthrylvinyl ketone* (III; X = 9-anthryl) condenses very readily with 9-anthraldehyde to give the di-condensation product. The condensation of 9-phenanthraldehyde with aqueous acetone in the presence of dilute sodium hydroxide also gave a mixture of products, which was separated by chromatography into (i) the desired *methyl 2-9′-phenanthrylvinyl ketone*, m. p. 85°, (ii) the hydroxy-ketone, *3-keto-1-9′-phenanthrylbutan-1-ol*, m. p. 119°, and (iii) a high-melting *dimer* of methyl 2-9′-phenanthrylvinyl ketone, m. p. 274°, probably to be formulated as a *cyclo*butane derivative by analogy with similar

dimers obtained from substituted styryl methyl ketones (Heilbron *et al.*, *J.*, 1927, 1888; 1928, 2323).

An alternative route to the 3-aryl-1-methylallyl alcohols is represented by the condensation of methylmagnesium bromide with the β-arylacraldehydes (V). The latter should be accessible *via* the arylaldehydes, but the reaction of acetaldehyde with both 1-naphthaldehyde and 9-anthraldehyde proved very sluggish. This is somewhat surprising in view of the high reactivity of the aryl aldehyde towards acetone (see above). In another attempt to prepare β-9′-anthrylacraldehyde (VI; X = 9-anthryl) *via* β-9′-anthrylacrylic acid, it was found that treatment of the acid with excess of thionyl chloride gave, not the required acid chloride, but a dichlorinated product which was readily hydrolysed to a monochloro-acid formulated as β-(10-*chloro*-9-*anthryl*)*acrylic acid*. This approach was not pursued.

The ultra-violet light-absorption data for the various derivatives are given in the table and in Figs. 1—4, and exhibit a number of interesting features. The absorptions of the 1-aryl-3-methylallyl alcohols (I) in this region are very similar to those of the unsubstituted polycyclic hydrocarbons, and practically identical with those of 1- and 2-methylnaphthalene, 9-methylanthracene and 9-methylphenanthrene severally, as far as these have been recorded (De Laszlo, *Z. physikal. Chem.*, 1925, **118**, 369; Jones, *Chem. Reviews*, 1947, **41**, 353; Askew, *J.*, 1935, 509). The spectral data thus provide very little evidence for any interaction between the aryl groups and the unconjugated ethylenic bond, such as observed (Braude, *J.*, 1949, 1902) in allylbenzene and certain related systems.

Ultra-violet light-absorption properties of 1-*aryl*-3-*methylallyl alcohols* (I), 3-*aryl*-1-*methylallyl alcohols* (II), *and methyl* 2-*arylvinyl ketones* (III) *in ethanol solution.*

(*c* = Concn. of absorbent in g.-mols./l. Cell thickness = 1 cm. throughout, except for X = Ph.)

		I.		II.		III.	
X.	*c*.	$\lambda_{max.}$, A.†	ε.	$\lambda_{max.}$, A.†	ε.	$\lambda_{max.}$, A.†	ε.
Phenyl [1,2]	—	2510	450	2480	19,000	2850	23,000
		2580	450	2510	19,500	—	—
		—	—	2810	2,000	—	—
		—	—	2910	1,550	—	—
1-Naphthyl	0·000021	2240	69,000 *	2280	51,000 *	2240	30,000
		2700	5,900	2960	10,000	2500	15,000
		2800	7,200	—	—	3300	11,500
		2900	5,200	—	—	—	—
	0·00021	3130	320	—	—	—	—
2-Naphthyl	0·000014	2260	95,000 *	*2390*	45,000 *	2370	16,500
		2740	6,300	2460	55,000 *	2450	16,500
		—	—	2540	50,000 *	*2650*	29,000
		—	—	*2750*	13,500	2720	32,000
		—	—	2840	16,500	3100	28,000
		—	—	2950	13,500	—	—
9-Anthryl	0·000012	2200	14,000	2200	10,500	2170	23,500
		2540	130,000 *	2550	115,000 *	2540	110,000
		3300	3,500	*3500*	6,000	3520	6,000
		3450	6,750	3600	8,500	3650	8,300
		3630	9,300	3820	9,000	3830	8,700
		3820	8,500	—	—	—	—
9-Phenanthryl	0·000021	*2440*	44,500	2400	34,500	2500	46,000
		2530	60,000	2570	48,000	3340	14,000
		2770	12,500	3010	13,500	—	—
		2950	11,000	*3050*	12,500		

* Strongly concentration-dependent.
† Figures in italics refer to inflections.
[1] Braude, Jones, and Stern, *J.*, 1946, 396.
[2] Lowry, Mouren, and MacConkey, *J.*, 1928, 3167.

With the 3-aryl-1-methylallyl alcohols (II), the bands are generally displaced towards longer wave-lengths, and the data for the naphthyl derivatives are very similar to those of 1-propenylnaphthalene (Pestemer and Manchen, *Monatsh.*, 1936, **68**, 92) and 2-vinylnaphthalene (Laitinen, Miller, and Parks, *J. Amer. Chem. Soc.*, 1947, **69**, 2707), respectively. The displacements are considerably smaller than those observed in comparing styrene with toluene, or cinnamyl alcohol with phenylvinylcarbinol. This is not unexpected since the additional conjugation due to the side-chain ethylenic group will be relatively smaller in the polycyclic systems. An exact comparison of the data for the unconjugated and conjugated derivatives is complicated by the vibrational structure of the bands, but for the purpose of discussion the

highest of the vibrational peaks may be taken as the centre of the particular band system. The bands of all the polycyclic derivatives fall into two groups, a high-intensity system (subsequently denoted by " E ") in the 2300—2600 A. region, and a low-intensity system (subsequently denoted by " B ") in the 2900—3600 A. region. With the conjugated 1-naphthyl derivatives, the displacements of the E bands are smaller than those of the B bands, whereas the reverse applies in the case of the 2-naphthyl derivatives. Somewhat related observations

Fig. 1. Fig. 2.

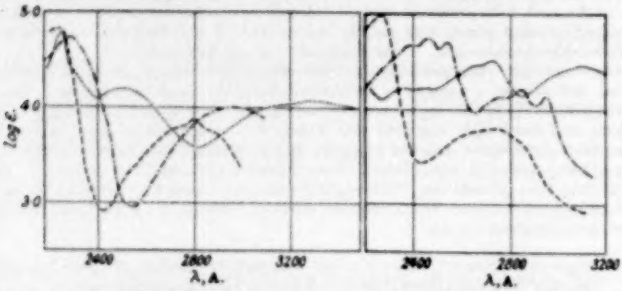


Fig. 1.—*Light absorption in ethanol of :* — — — — 1-(1-*Naphthyl*)-3-*methylallyl alcohol*.
— · — · — 3-(1-*Naphthyl*)-1-*methylallyl alcohol*.
– – – – – *Methyl* 2-1′-*naphthylvinyl ketone*.

Fig. 2.—*Light absorption in ethanol of :* — — — — 1-(2-*Naphthyl*)-3-*methylallyl alcohol*.
— · — · — 3-(2-*Naphthyl*)-1-*methylallyl alcohol*.
– – – – – *Methyl* 2-2′-*naphthylvinyl ketone*.

Fig. 3. Fig. 4.

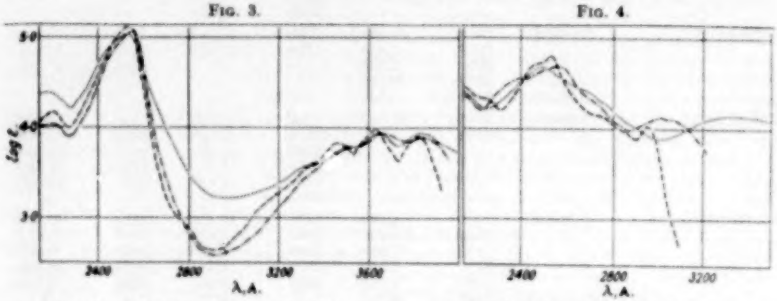


Fig. 3.—*Light absorption in ethanol of :* — — — — 1-(9-*Anthryl*)-3-*methylallyl alcohol*.
— · — · — 3-(9-*Anthryl*)-1-*methylallyl alcohol*.
– – – – – *Methyl* 2-9′-*anthrylvinyl ketone*.

Fig. 4.—*Light absorption in ethanol of :* — — — — 1-(9-*Phenanthryl*)-3-*methylallyl alcohol*.
— · — · — 3-(9-*Phenanthryl*)-1-*methylallyl alcohol*.
– – – – – *Methyl* 2-9′-*phenanthrylvinyl ketone*.

have been made by Jones (*loc. cit.*), who found that in anthracene derivatives, conjugating substituents in the 9-position produce smaller displacements of the E than of the B bands, whereas the reverse applies in the case of conjugating substituents in the 2-position. Jones put forward a tentative explanation of his observations in terms of the linear electronic oscillator model (Lewis and Calvin, *Chem. Reviews*, 1939, **25**, 273), assuming that the E and B bands arise from transitions polarised along the longer and shorter axis of the molecule, respectively. This assignment is in agreement with that deduced by Coulson (*Proc. Physical Soc.*, 1948, **60**, 257) from molecular-orbital calculations. The present observations on the spectral effects of an ethylenic substituent in the 1- and the 2-position of naphthalene may be explained in a similar

way.* Another effect shown by the polycyclic derivatives in contrast to their phenyl analogues is that only the intensity of the B bands is increased, whilst that of the E bands is reduced, by the conjugated ethylenic group.

The absorption of 3-9′-phenanthryl-1-methylallyl alcohol exhibits bathochromic displacements similar to those of the 1-naphthyl derivative. 3-9′-Anthryl-1-methylallyl alcohol, on the other hand, differs from the other members of the series in that the wave-length locations of the maxima are practically identical with those of the unconjugated isomer, 1-9′-anthryl-3-methylallyl alcohol; moreover, the intensities of all the bands are considerably reduced as compared with the unconjugated isomer. A similar lack of spectral interaction has been observed by Jones (*loc. cit.*) in 9-phenylanthracene, and ascribed to the non-coplanarity of the phenyl and the anthryl groups owing to steric interference between the *o*-hydrogen atoms of the former and the 1- and 8-hydrogen atoms of the latter. Many other examples of the manifestation of steric inhibition of resonance in spectral properties have been described (for a summary and discussion, see Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890) and there can be little doubt that the anomalous absorption of 3-9′-anthryl-1-methylallyl alcohol also arises in this way. It will be observed that 3-9′-phenanthryl-1-methylallyl alcohol appears to exhibit normal absorption although free rotation should again be hindered; in this case, however, interference will only occur with the 8-hydrogen atom on one " side " of the molecule and a coplanar configuration is possible when the end of the side chain is inclined towards the 10-position.

The absorptions of the methyl 2-arylvinyl ketones (III) exhibit relationships similar to those shown by the 3-aryl-1-methylallyl alcohols and need not be discussed in detail. As would be expected, the bathochromic displacements are somewhat greater with the ketones than with the alcohols, but very much smaller than those shown by the phenyl analogue, styryl methyl ketone. The absorption of the 9-anthryl derivative again shows an almost complete lack of bathochromic displacements, probably owing to steric hindrance. The same effect is observed in the structurally related *oo′*-dimethylstyryl methyl ketone (Braude, Jones, and Sondheimer, forthcoming publication).

Another interesting feature associated with the spectra of the polycyclic derivatives is that the intensity of some of the bands appears to be strongly concentration-dependent (see Table I). This phenomenon is also shown in varying degrees by the parent hydrocarbons and is due to the superposition of absorption and fluorescence-emission (Braude, Fawcett, and Timmons, *J.*, in the press). The fluorescence activity of the different bands varies greatly; it is particularly marked in the high-intensity (E) bands of the anthryl derivatives and naphthylcarbinols, but almost absent in the phenanthryl derivatives and the methyl 2-naphthylvinyl ketones. Solutions of 3-9′-anthryl-1-methylallyl alcohol exhibit strong visible fluorescence in daylight.

Experimental.

(Light-absorption data are only given when not included in Table I.)

1-1′-Naphthyl-3-methylallyl Alcohol (I; X = 1-Naphthyl).—Freshly distilled crotonaldehyde (35 g.) in ether (100 ml.) was added to 1-naphthylmagnesium bromide (from magnesium, 12 g., and 1-bromonaphthalene, 104 g.) in ether (500 ml.) during 2 hours at 0° in an atmosphere of nitrogen. Stirring was continued for 2 hours and excess of saturated ammonium chloride solution was then added during ½ hour at 0°. The ethereal layer was separated, dried (Na_2SO_4), and distilled in a high vacuum from a trace of anhydrous potassium carbonate. A small amount of naphthalene (*ca.* 0·5 g.) sublimed first and then *1-1′-naphthyl-3-methylallyl alcohol* (61 g., 62%) distilled as viscous oil, b. p. 110° (bath)/10^{-4} mm., n_D^{25} 1·6218 (Found: C, 85·0; H, 7·1. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%). Shurakowski (*J. Phys. Chem. Russia*, 1909, **41**, 1687) gives b. p. 204—206°/22 mm. The *p-nitrobenzoate* separated from light petroleum (b. p. 60—80°) in colourless crystals, m. p. 118—119° (Found: N, 4·1. $C_{21}H_{17}O_4N$ requires N, 4·0%). Light absorption in ethanol: Maxima, 2230 and 2640 A., ε = 67,000 and 19,000, respectively. On prolonged storage in contact with air, the carbinol is slowly converted into the conjugated isomer (below), as a result of the formation of small amounts of acidic oxidation products.

3-1′-Naphthyl-1-methylallyl Alcohol (II; X = 1-Naphthyl).—(*a*) 1-1′-Naphthyl-3-methylallyl alcohol (5 g.) was dissolved in 60% aqueous acetone–0·1N-hydrochloric acid (200 ml.), and the solution kept for 24 hours at room temperature. On dilution with water *3-1′-naphthyl-1-methylallyl alcohol* (4·5 g.) separated as an oil, which was distilled at 95° (bath)/10^{-4} mm. It solidified on storage at 0° and crystallised from pentane in colourless plates, m. p. 41—42° (Found: C, 85·1; H, 7·3. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%). The *p-nitrobenzoate* crystallised from light petroleum (b. p. 60—80°) in very pale yellow needles, m. p. 93° (Found: C, 73·0; H, 5·0; N, 4·1. $C_{21}H_{17}O_4N$ requires C, 72·6; H, 4·9; N, 4·0%). Light absorption in ethanol: Maxima, 2280, 2600, and 2910 A., ε = 61,000, 17,500, and 14,000, respectively.

* Since this paper was written, a longitudinal polarisation of the 2300 A. band and a transverse polarisation of the 2900 A. band of naphthalene have also been deduced by Klovens and Platt (*J. Chem. Physics*, 1949, **17**, 470).

(*b*) 1-1′-Naphthyl-3-methylallyl alcohol (5 g.) was dissolved in 90% aqueous acetone–0·1*N*-hydrochloric acid (75 ml.), and the solution kept *for* 24 hours at room temperature. On dilution with water an oil separated, which was distilled at 10^{-4} mm., giving 3-1′-naphthyl-1-methylallyl alcohol, b. p. 95° (bath) (1·5 g., 30%), and a high-boiling fraction, b. p. 250° (bath) (2·75 g., 55%). On cooling, the high-boiling fraction set to a glassy solid which failed to react with sodium or methylmagnesium iodide in ether. On the basis of this evidence and the analytical and light-absorption data it is formulated as 1-1′-*naphthyl*-3-*methylallyl* 3-1′-*naphthyl*-1-*methylallyl ether* (Found : C, 88·4; H, 6·9. $C_{32}H_{30}O$ requires C, 88·8; H, 6·9%). Light absorption in ethanol : Maxima, 2260 and 2820 A., ε = 130,000 and 17,000, respectively.

Methyl 2-1′-*Naphthylvinyl Ketone* (III ; X = 1-Naphthyl).—(*a*) 1-Naphthaldehyde (4 g. ; Hinkel, Ayling, and Beynon, *J.*, 1936, 342), acetone (30 ml.), and 1% sodium hydroxide (100 ml.) were stirred together at 40° for 24 hours. Ether extraction and distillation yielded the ketone (4 g., 80%), b. p. 142°/5 × 10^{-4} mm., n_D^{20} 1·6670 (Wilds *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 1985, give b. p. 163—173°/0·9 mm., n_D^{25} 1·6665). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine in needles, m. p. 261° (Found : C, 64·0; H, 4·4; N, 15·0. $C_{26}H_{18}O_4N_4$ requires C, 63·8; H, 4·3; N, 14·9%). Light absorption in chloroform : Maxima, 2560, 3230, and 3970 A., ε = 32,500, 16,000, and 37,500, respectively.

(*b*) 3-1′-Naphthyl-1-methylallyl alcohol (2 g.), aluminium *tert.*-butoxide (2·5 g.), dry acetone (20 ml.), and benzene (20 ml.) were refluxed together for 24 hours. Decomposition with excess of sulphuric acid, ether-extraction, and distillation yielded 1-naphthylmethyleneacetone, b. p. 85°/10^{-4} mm., n_D^{20} 1·6580 (1·3 g., 65%), which gave a 2 : 4-dinitrophenylhydrazone, m. p. 261°, undepressed on admixture with the authentic specimen.

1-2′-*Naphthyl*-3-*methylallyl Alcohol* (1 ; X = 2-Naphthyl).—2-Bromonaphthalene (52 g., Newman and Wise, *J. Amer. Chem. Soc.*, 1941, **63**, 2847) in ether (200 ml.) was added slowly to a suspension of magnesium (6 g.) in ether (200 ml.) containing ethyl bromide (0·5 g.), and the mixture was stirred for 2 hours in an atmosphere of nitrogen. Freshly distilled crotonaldehyde (18 g.) in ether (30 ml.) was then added slowly at 0°, and stirring continued for a further 3 hours. Decomposition of the Grignard complex with ammonium chloride solution, isolation of the product in the usual manner, and distillation from a trace of anhydrous potassium carbonate afforded 2 : 2′-dinaphthyl, m. p. 175° (0·5 g.), and 1-2′-*naphthyl*-3-*methylallyl alcohol* (27 g., 55%), b. p. 90° (bath)/10^{-4} mm., n_D^{20} 1·6190, which solidified when kept and crystallised from pentane in fine needles, m. p. 43—44° (Found : C, 84·8; N, 7·1. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%).

3-2′-*Naphthyl*-1-*methylallyl Alcohol* (II ; X = 2-Naphthyl).—1-2′-Naphthyl-3-methylallyl alcohol (5 g.) was dissolved in 60% aqueous acetone–0·1*N*-hydrochloric acid (200 ml.), and the solution kept for 24 hours at room temperature. On dilution with water, 3-2′-*naphthyl*-1-*methylallyl alcohol* (4·8 g.) separated. It crystallised from light petroleum (b. p. 40—60°) in fine needles, m. p. 94° (Found : C, 85·1; H, 7·1. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%). The p-*nitrobenzoate* separated from light petroleum (b. p. 80—100°) in crystals, m. p. 113° (Found : C, 72·7; H, 5·1; N, 4·0. $C_{21}H_{17}O_4N$ requires C, 72·6; H, 4·9; N, 4·0%). Light absorption in chloroform : Maxima, 2510, 2570, 2700, 2780, 2890, 2990, and 3410 A., ε = 55,500, 28,000, 21,500, 19,000, 15,500, and 1,100, respectively.

Methyl 2-2′-*Naphthylvinyl Ketone* (III ; X = 2-Naphthyl).—3-2′-Naphthyl-1-methylallyl alcohol (2·5 g.), aluminium *tert.*-butoxide (3 g.), dry acetone (30 ml.), and benzene (30 ml.) were refluxed together for 24 hours. Decomposition with sulphuric acid gave the ketone (1·5 g.), which separated from methanol as crystals, m. p. 103—104° (Wilds *et al.*, *loc. cit.*, give m. p. 104°). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine in needles, m. p. 268° (Found : C, 64·1; H, 4·5; N, 14·9. $C_{26}H_{18}O_4N_4$ requires C, 63·8; H, 4·3; N, 14·9%). Light absorption in chloroform : Maxima, 3160 and 3980 A., ε = 19,000 and 37,500, respectively.

1-9′-*Anthryl*-3-*methylallyl Alcohol* (1 ; X = 9-Anthryl).—9-Bromoanthracene (26 g., Barnett and Cook, *J.*, 1924, **125**, 1084) in ether (200 ml.) was refluxed with ethyl bromide (11 g.) and magnesium (4·9 g.) for 24 hours. Freshly distilled crotonaldehyde (14 g.) in ether (50 ml.) was then added slowly to the ice-cold suspension, and stirring continued for 1 hour. Decomposition of the Grignard complex with ammonium chloride, and isolation of the product afforded 1-9′-*anthryl*-3-*methylallyl alcohol* (17 g., 68%), which crystallised from hot ethyl acetate–light petroleum (b. p. 40—60°) in very pale yellow crystals, m. p. 114° (Found : C, 87·0; H, 6·4. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%).

3-9′-*Anthryl*-1-*methylallyl Alcohol* (II ; X = 9-Anthryl).—1-9′-Anthryl-3-methylallyl alcohol (5 g.) was dissolved in 60% aqueous acetone–0·1*N*-hydrochloric acid, and the solution kept for 24 hours at room temperature. On dilution with water, 3-9′-*anthryl*-1-*methylallyl alcohol* (4·9 g.) separated. It crystallised from light petroleum (b. p. 40—60°) in yellow needles, m. p. 116° (Found : C, 86·9; H, 6·65. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%). The p-*nitrobenzoate* crystallised from light petroleum (b. p. 80—100°) in orange needles, m. p. 150° (Found : C, 75·6; H, 5·0; N, 3·6. $C_{25}H_{19}O_4N$ requires C, 75·6; H, 4·8; N, 3·5%). Light absorption in ethanol : Maxima, 2560, 3510, 3670, and 3860 A., ε = 155,000, 6,500, 8,500, and 7,100, respectively.

Methyl 2-9′-*Anthrylvinyl Ketone* (III ; X = 9-Anthryl).—(*a*) A mixture of 9-anthraldehyde (2 g. ; Fieser, Hartwell, and Jones, *Org. Synth.*, **20**, 11), acetone (20 ml.), and 10% sodium hydroxide (1 ml.) was kept at room temperature for 24 hours. Filtration yielded 1 : 5-*di*-9′-*anthrylpenta*-1 : 4-*dien*-3-*one* (0·4 g., 18%), which crystallised from pyridine in orange plates, m. p. 293° (Found : C, 91·2; H, 4·9. $C_{33}H_{22}O$ requires C, 91·2; H, 5·1%). Light absorption in chloroform : Maxima, 2520, 2560, and 3850 A., ε = 14,500, 14,500, and 13,500, respectively. Addition of water to the filtrate gave *methyl* 2-9′-*anthrylvinyl ketone* (1·4 g., 56%), which crystallised from ethanol in yellow needles, m. p. 113° (Found : C, 88·0; H, 5·8. $C_{19}H_{14}O$ requires C, 87·6; H, 5·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine in needles, m. p. 244° (Found : C, 67·5; H, 4·2; N, 13·1. $C_{25}H_{18}O_4N_4$ requires C, 67·6; H, 4·3; N, 13·1%). Light absorption in chloroform : Maxima, 4080 A., ε = 22,500. On one occasion, a different di-condensation product, probably a stereoisomeric 1 : 5-*di*-9′-*anthrylpenta*-1 : 4-*dien*-3-*one*, m. p. 268°, was obtained (Found : C, 91·4; H, 5·4. $C_{33}H_{22}O$ requires C, 91·2; H, 5·1%). Light absorption in chloroform : Maxima 2510, 2560, and 3680 A., ε = 110,000, 105,000, and 7,200 respectively.

(*b*) 3-9′-Anthryl-1-methylallyl alcohol (0·8 g.), aluminium *tert.*-butoxide (2 g.), dry acetone (10 ml.),

and benzene (10 ml.) were refluxed together for 24 hours. Decomposition with sulphuric acid and ether extraction gave a viscous oil, which crystallised from ethanol to give **methyl 2-9′-anthryivinyl ketone**, m. p. 112°, undepressed on admixture with the authentic specimen.

1 : 5-*Di-9′-anthrylpenta*-1 : 4-*dien*-3-*one*.—A solution of 9-anthrylmethylenacetone (0·5 g.) and 9-anthraldehyde (0·5 g.) in dry ethyl acetate (10 ml.) was saturated with dry hydrogen chloride and kept for 2 hours. The 1 : 5-di-9′-anthrylpenta-1 : 4-dien-3-one (0·8 g.) was filtered off, and crystallised from pyridine in orange plates, m. p. 291°, undepressed on admixture with the specimen obtained above.

1-9′-*Phenanthryl*-3-*methylallyl alcohol* (I; X = 9-Phenanthryl).—9-Bromophenanthrene (21 g.; Austin, *J.*, 1908, **93**, 1763) and ethyl bromide (9 g.) in a mixture of benzene (100 ml.) and ether (100 ml.) were added slowly to a suspension of magnesium (4 g.) in ether (100 ml.), stirred for 1 hour and then refluxed for 7 hours. Freshly distilled crotonaldehyde (11·5 g.) in ether (50 ml.) was added slowly at 0°, and stirring continued for 2 hours. Decomposition of the Grignard complex with ammonium chloride, isolation of the product, and vacuum distillation gave an oil which did not solidify. This was chromatographed from benzene solution on an alumina column, a mixture of benzene and ethanol being used as eluent, to give solid 1-9′-*phenanthryl*-3-*methylallyl alcohol* (15 g., 75%), which crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 88—89° (Found: C, 86·8; H, 6·4. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%).

3-9′-*Phenanthryl*-1-*methylallyl Alcohol* (II; X = 9-Phenanthryl).—1-9′-Phenanthryl-3-methylallyl alcohol (3 g.) was dissolved in 60% aqueous acetone–0·1N-hydrochloric acid (200 ml.), and the solution set aside for 24 hours at room temperature. On dilution with water 3-9′-*phenanthryl*-1-*methylallyl alcohol* (2·7 g.) separated. It crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 103° (Found: C, 87·3; H, 6·6. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%). The *p-nitrobenzoate* crystallised from *cyclo*hexane in colourless needles, m. p. 122° (Found: C, 75·9; H, 4·8; N, 3·7. $C_{32}H_{21}O_4N$ requires C, 75·6; H, 4·8; N, 3·5%). Light absorption in ethanol: Maxima, 2550 and 3050 A., ε = 53,500 and 15,000, respectively.

Methyl* 2-9′-*Phenanthrylvinyl Ketone (III; X = 9-Phenanthryl).—3-9′-Phenanthryl-1-methylallyl alcohol (1 g.) and aluminium *tert.*-butoxide (2 g.) in dry acetone (10 ml.) and benzene (10 ml.) were refluxed for 24 hours. Decomposition with sulphuric acid and ether extraction gave a viscous oil, which crystallised from ethanol to give the ketone (0·6 g., 60%). The 2 : 4-dinitrophenylhydrazone crystallised from pyridine in needles, m. p. 268°, undepressed on admixture with the authentic specimen obtained below.

Reaction between **9-*Phenanthraldehyde* and *Acetone*.**—A mixture of 9-phenanthraldehyde (3 g.; Miller and Bachman, *J. Amer. Chem. Soc.*, 1935, **57**, 766), acetone (40 ml.), and 10% sodium hydroxide (1 ml.) was kept at room temperature for 24 hours. Addition of water to the mixture gave a viscous gum which did not solidify. This was chromatographed from benzene solution on an alumina column to give 3 products as follows.

(i) ***Methyl* 2-9′-*phenanthrylvinyl ketone*** (1·5 g., 40%), which crystallised from aqueous acetone in pale yellow crystals, m. p. 85° (Found: C, 87·5; H, 5·8%; *M*, in camphor, 251. $C_{19}H_{14}O$ requires C, 87·9; H, 5·7%; *M*, 246). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine in needles, m. p. 269° (Found: C, 67·7; H, 4·4; N, 12·9. $C_{25}H_{18}O_4N_4$ requires C, 67·6; H, 4·3; N, 13·1%). Light absorption in chloroform: Maxima, 2560, 3240, and 2980 A., ε = 57,000, 14,500, and 38,000, respectively.

(ii) **3-*Keto*-1-9′-*phenanthrylbutan*-1-*ol*** (0·96 g., 25%), which crystallised from light petroleum (b. p. 80—100°) in colourless needles, m. p. 119° (Found: C, 82·1; H, 6·3. $C_{19}H_{16}O_2$ requires C, 81·9; H, 6·1%). Light absorption in ethanol: Maxima, 2530, 2970, 3250, 3320, 3410, and 3480 A., ε = 71,000, 13,000, 290, 330, 260, and 290, respectively. The 2 : 4-*dinitrophenylhydrazone* separated from aqueous pyridine in orange crystals, m. p. 256° (Found: C, 65·0; H, 4·7; N, 12·8. $C_{25}H_{20}O_5N_4$ requires C, 64·9; H, 4·5; N, 12·6%). Light absorption in chloroform: Maxima, 2560, 2960, 2990, and 3600 A., ε = 67,000, 13,500, 14,500, and 22,000, respectively.

(iii) A *dimer* of methyl 2-9′-phenanthrylvinyl ketone (0·4 g., 10%), which separated from pyridine as colourless plates, m. p. 274° (Found: C, 87·7; H, 6·0; *M*, in camphor, 450. $C_{38}H_{28}O_2$ requires C, 87·8; H, 5·7%; *M*, 492). Light absorption in chloroform: Maxima, 2580, 2800, 2910, and 3010 A., ε = 125,000, 27,000, 23,000, and 28,000, respectively.

Reaction between ***Anthrylacrylic Acid* and *Thionyl Chloride*.**—Anthrylacrylic acid (2 g.; Davis and Carmack, *J. Org. Chem.*, 1947, **12**, 76) was refluxed with thionyl chloride (1·7 g.) for 30 minutes. The product solidified on cooling and crystallised from benzene in yellow-brown needles, m. p. 204° (1·8 g., 75%), and is formulated as ***β*-(9-*chloro*-10-*anthryl*)*acryloyl chloride*** (Found: C, 67·4; H, 3·5. $C_{17}H_{10}OCl_2$ requires C, 67·8; H, 3·3%). The acid chloride (1·8 g.) was refluxed with 10% potassium hydroxide (20 ml.) for 30 minutes. The reaction mixture was acidified, and crystallisation of the product from nitrobenzene gave a chloro-acid, m. p. 264° (1·6 g., 95%), formulated as ***β*-(9-*chloro*-10-*anthryl*)*acrylic acid*** (Found: C, 72·1; H, 4·2. $C_{17}H_{11}O_2Cl$ requires C, 72·2; H, 3·9%). Light absorption in ethanol: Maxima, 2580, 3770, and 3970 A., ε = 155,000, 9,600, and 9,400, respectively.

Reaction between **1-*Naphthaldehyde* and *Acetaldehyde*.**—Acetaldehyde (2 g.) was slowly added to a stirred solution of 1-naphthaldehyde (2 g.) and 10% sodium hydroxide (2 ml.) in aqueous methanol (20 ml.). Ether extraction of the reaction mixture gave an oil, which on distillation gave unchanged 1-naphthaldehyde (0·5 g.) and a high-boiling fraction which did not solidify. Similar results were obtained when using piperidinium acetate as a catalyst.

Reaction between **9-*Anthraldehyde* and *Acetaldehyde*.**—Acetaldehyde (2 g.) was caused to react with 9-anthraldehyde (2 g.) under similar conditions to the above. Ether extraction gave a gum which could not be solidified.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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159. *The Kinetics of Anionotropic Rearrangement. Part IX. The Effects of Polycyclic Aromatic Substituents on Reactivity. A Comparison of the Electronic Properties of the Phenyl, 1-Naphthyl, 2-Naphthyl, 9-Anthryl, and 9-Phenanthryl Groups.*

By E. A. Braude and J. S. Fawcett.

The kinetics of the acid-catalysed oxotropic rearrangements of a number of polycyclic 1-aryl-3-methylallyl alcohols (I) to the corresponding 3-aryl-1-methylallyl alcohols (II) have been determined in aqueous dioxan solution. The results are compared with those previously obtained for the rearrangement of 1-phenyl-3-methylallyl alcohol (phenylpropenylcarbinol) (I; X = Ph) and appear to provide the first comprehensive set of quantitative kinetic data on a series of polycyclic aromatic derivatives. The rate constants at one temperature increase in the sequence 9-phenanthryl < phenyl < 2-naphthyl ~ 1-naphthyl < 9-anthryl, but the differences are relatively small and there is little variation in either the energies of activation or the probability factors.

The results are discussed in relation to existing evidence concerning the reactivity of polycyclic aromatic systems. Qualitatively, they are in agreement with the predictions of both valency-bond resonance and molecular-orbital theory, except for the phenanthryl derivative. An explanation for this anomaly is suggested. Quantitatively, the results for the naphthyl and anthryl derivatives show a closer correlation with simple valency-bond resonance theory than with molecular-orbital calculations, and a linear relation is found to hold between the rate constants at one temperature and the expected number of contributing polar resonance forms.

In earlier work in this series (Part V, *J.*, 1946, 396; Part VI, *J.*, 1947, 1096; Part VIII, *J.*, 1948, 1982), the rearrangement of 1-phenyl-3-methylallyl alcohol (phenylpropenylcarbinol) (I; X = Ph) to 3-phenyl-1-methylallyl alcohol (styrylmethylcarbinol) (II; X = Ph) has been investigated in some detail. The isomerisation proceeds with great facility and without side reactions in dilute acid solution, and its mechanism under these conditions can now be regarded as established with a reasonable degree of certainty. It has also been shown that this type of rearrangement is very sensitive to structural changes, being facilitated by electron-donating

(I.) X·CH(OH)·CH:CHMe ⟶ X·CH:CH·CH(OH)·Me (II.)

and hindered by electron-attracting substituents, as required by its mechanism. Since a wide variety of analogues of 1-phenyl-3-methylallyl alcohol is fairly readily accessible synthetically, this affords an excellent basis for investigating the electronic properties of substituents which have not yet been studied in this respect because of a lack of suitable reactions or for other reasons. This applies to a surprisingly large number of common and important groups. Polycyclic and heterocyclic organic chemistry, in particular, are almost devoid of quantitative reactivity data, and theoretical work has considerably outstripped experimental advances in this field.

The present communication deals with a kinetic study of the rearrangements of some polycyclic 1-aryl-3-methylallyl alcohols (I; X = 1-naphthyl, 2-naphthyl, 9-anthryl, and 9-phenanthryl), the synthesis and rearrangements of which have been described (Braude, Fawcett, and Newman, preceding paper). The rate constants, energies of activation, and probability factors under standard conditions employed in earlier studies are collected in Tables I and II. As before, the reaction rates were determined spectrometrically, advantage being taken of the differences between the ultra-violet light absorption of 1-aryl-3-methylallyl and the isomeric 3-aryl-1-methylallyl alcohols. A complication arose with the 9-anthryl derivative owing to the intense fluorescence of the rearranged carbinol, but this could be overcome by suitable choice of wave-lengths (see Experimental). Good first-order rate constants were obtained throughout, and the final absorption intensities at the wave-lengths chosen were identical within experimental error with those of the pure 3-aryl-1-methylallyl alcohols, showing that no measurable equilibria were set up. The usual solvent effects were observed, the rate constants being decreased about threefold, and the Arrhenius energies of activation increased by about 3 kcals./mol., in 80% as compared with 60% aqueous dioxan. The rate constants at one temperature increase in the sequence 9-phenanthryl < phenyl < 2-naphthyl ≃ 1-naphthyl < 9-anthryl, but the differences are small and only cover a range of fivefold variation. The values for the two naphthyl derivatives lie especially close together and their order depends on the temperature, the rearrangement of the 1-naphthyl derivative being a little faster below 50°, and a little slower above 50°, than that of the 2-naphthyl derivative. The Arrhenius energies of activation and probability factors for a particular medium are practically constant

throughout the series; the differences in energy of activation only slightly exceed the uncertainty in the Arrhenius plots (ca. ±0·3 kcal./mol.).

The rearrangement of the lower homologues, 1-naphthyl- and 2-naphthyl-vinylcarbinol, has been examined qualitatively by Burton (*J.*, 1931, 759), who concluded from indirect evidence (the degree of rearrangement accompanying *p*-nitrobenzoylation) that the ease of isomerisation increases in the order phenyl < 2-naphthyl < 1-naphthyl.

TABLE I.

First-order rate constant (10^4 k, *min.*$^{-1}$) *for the rearrangements of* 1-*aryl*-3-*methylallyl alcohols* (I) *to* 3-*aryl*-1-*methylallyl alcohols* (II) *in aqueous dioxan–0·01*M-*hydrochloric acid.*

[Concentration of alcohols, 0·001—0·01M.; c_d = dioxan concentration (% v/v).]

Temp.	c_d.*	X = Phenyl.[1]	2-Naphthyl.	1-Naphthyl.	9-Anthryl.	9-Phenanthryl.
0°	60	*5·4*	8·0	8·3	25	4·0
30	60	184	320	345	905	146
	80	69	126	129	315	66
40	60	545	900	840	2,050	445
	80	—	400	405	1,050	210
50	60	1510	2450	2450	6,500	1280
	80	—	1300	1180	3,200	700
60	60	3650	6100	5300	14,500	3200
	80	—	3300	2900	6,650	1890

* Values for c_d = 80% at 0° are omitted, as solid dioxan tended to crystallise in the media.
[1] Braude, Jones, and Stern, *J.*, 1946, 396. The value for c_d = 80% at 30° is extrapolated from measurements at higher acid concentrations.

TABLE II.

Relative rate constants (r), *Arrhenius energies of activation, and probability factors.*

($k/c_A = Ae^{-E_{Arr.}/RT}$, where c_A = acid concentration.)

	60% Aqueous dioxan.			80% Aqueous dioxan.		
X.	r.*	$E_{Arr.}$	log *A*.	r.*	$E_{Arr.}$	log *A*.
Phenyl[1]	1	19·5	12·6	1	—	—
2-Naphthyl	1·74	20·2	13·3	1·82	22·4	14·5
1-Naphthyl	1·88	19·9	13·1	1·87	22·0	14·2
9-Anthryl	4·37	19·5	13·2	6·32	22·0	14·6
9-Phenanthryl	0·80	20·3	13·1	0·96	22·6	14·4
(Vinyl[2])	0·78	—	—	0·67	—	—

* At 30°.
[1] Braude, Jones, and Stern, *loc. cit.*
[2] Braude and Jones, *J.*, 1946, 128. (Extrapolated from measurements in aqueous ethanol.)

DISCUSSION.

(1) *Correlation of Available Data on the Reactivity of Polycyclic Aromatic Compounds.*—The reactivity of the polycyclic aromatic hydrocarbons is generally stated to increase in the order benzene < naphthalene < phenanthrene < anthracene. This sequence is based on a wealth of *qualitative* data concerning, particularly, the ease of sulphonation, nitration, bromination, hydrogenation, and oxidation, and although it is a commonplace that such qualitative comparisons of reactivity without kinetic control can be misleading, there is no reason to doubt the validity of the general result in the present case. The reactions enumerated above include both heterolytic and homolytic types, and it is of some interest that the different types of reactivity appear to run parallel in this series; however, we are here concerned only with heterolytic reactivity and therefore confine attention to sulphonation and nitration which almost certainly involve attack by the entities SO_3H^+ and NO_2^+ under the usual conditions (for references, see Braude, *Ann. Reports*, 1949, **46**, in the press). The results for naphthalene are clear-cut, both sulphonation and nitration proceeding with comparable speed at lower temperatures than those required for benzene, and substitution in the 1- being somewhat faster than in the 2-position. Phenanthrene is sulphonated and nitrated with comparable speed at a lower temperature than naphthalene, but the evidence concerning the reactivity of the different positions is somewhat conflicting; it appears that the 9-, 2-, and 3-positions are most readily substituted, with the reactivity probably decreasing in that order (cf. Fieser, *J. Amer. Chem. Soc.*, 1929, **51**, 2460). Finally, anthracene undergoes electrophilic substitution somewhat more readily still, but here sulphonation is faster in the 1- and 2-positions, whereas nitration is fastest in the 9-position. The abnormal orientation of the sulphonation of anthracene is probably due

to steric hindrance which will first become effective at the " flanked " *meso*-positions and with large reagents, such as SO_3H^-.

Some kinetic measurements on the halogenation of polycyclic aromatic hydrocarbons have been recorded (Lauer and Oda, *Ber.*, 1936, **69**, 141, 146, 851; Robertson, De La Mare, and Johnston, *J.*, 1943, 276; De la Mare and Robertson, *ibid.*, p. 279; Wibaut and Sixma, *Proc. K. Akad. Wetensch. Amsterdam*, 1948, **51**, 776), but they do not readily lend themselves to comparison owing to the different conditions employed and owing to the incursion of catalytic effects; the brominations of anthracene and phenanthrene are further complicated by the simultaneous occurrence of substitution and addition reactions (Price, *J. Amer. Chem. Soc.*, 1936, **58**, 1834, 2101; Fieser and Price, *ibid.*, p. 1838).

Most of the scant *quantitative* data to be found in the literature regarding the reactivity of polycyclic aromatic compounds, as well as the present results, concern side-chain reactions (see Table III). Shoesmith and Rubli (*J.*, 1927, 3098) and Ingold and Patel (*J. Indian. Chem. Soc.*, 1930, **7**, 95) investigated the neutral hydrolysis and alcoholysis of benzyl, 2-naphthylmethyl, and 1-naphthylmethyl bromides in 90% aqueous alcohol and obtained rate constants increasing in that order. Bergmann and Hirshberg (*J.*, 1936, 331) determined the rates of alkaline hydrolysis of methyl 1- and methyl 2-naphthoate in aqueous methanol of unstated composition and found that the 1- reacted slightly faster than the 2-naphthyl ester. The rate constants for both naphthyl derivatives are smaller than a quoted value for methyl benzoate, but this comparison may not be significant since the solvent conditions are not necessarily identical. Recently, Gordon, Miller, and Day (*J. Amer. Chem. Soc.*, 1948, **70**, 1946; 1949, **71**, 1245) have measured the rates of ammonolysis of alkyl and aryl acetates in anhydrous ethylene glycol and found that the naphthyl esters react about 100 times more *slowly* than phenyl acetate. The effective reagent in this reaction is believed to be a relatively large ammonia–glycol complex, and the exceptionally low reactivity of the polycyclic derivatives is ascribed to steric hindrance. The only previous kinetic data for polycyclic systems other than naphthyl derivatives appear to come from Shoppee's study (*J.*, 1933, 40) of the reversible prototropic rearrangements of 1-phenyl-3-arylmethylenazomethines. The order of mobilities was found to be 9-phenanthryl < 2-naphthyl < 1-naphthyl, but no value could be obtained for the phenyl substituent since the 1 : 3-diphenyl derivative is completely symmetrical.

TABLE III.

Relative reactivities (reaction rates) of polycyclic aromatic derivatives.

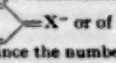
X.	(1).	(2).	(3).	(4).	(5).	(6).
Phenyl	[1]	1	—	1	—	1
2-Naphthyl	[2]	1·74	0·88	1·68	0·83	0·01
1-Naphthyl	[3]	1·88	1	2·16	1	0·01
9-Anthryl	[5]	4·37	—	—	—	—
9-Phenanthryl	[4]	0·80	0·65	—	—	—
(Vinyl)	—	0·78	—	—	—	0·24

(1) Sequence of ease of nitration of hydrocarbons derived from qualitative data. (2) Oxotropic rearrangement of 1-aryl-3-methylallyl alcohols at 30° (this paper). (3) Prototropic rearrangement of 1-phenyl-3-arylmethylenazomethines at 90° (Shoppee, *loc. cit.*). (4) Neutral hydrolysis of arylmethyl bromides at 25° (Shoesmith and Rubli, *loc. cit.*). (5) Alkaline hydrolysis of methyl naphthoates at 60° (Bergmann and Hirshberg, *loc. cit.*). (6) Ammonolysis of aryl acetates at 30° (Gordon, Miller, and Day, *loc. cit.*).

Summarising the available evidence, and neglecting exceptions probably conditioned by steric hindrance, we find the same order of increasing heterolytic reactivity, phenyl < 2-naphthyl < 1-naphthyl < 9-anthryl, to apply to both nuclear and side-chain reactions. The position of the 9-phenanthryl group, on the other hand, varies; it is below 9-anthryl in nuclear cationoid substitution, below naphthyl (and possibly phenyl) in side-chain prototropy, and below phenyl in side-chain oxotropy.

(2) *Qualitative Theory.*—The generally accepted basis of the electronic theory of substituent effects is that substituents increase or decrease, as the case may be, the electron-availability at the point of reaction and thereby increase or decrease the energy of activation (E) of the heterolytic fission, depending on the electronic requirements of the latter (cf. Hinshelwood, Laidler, and Timm, *J.*, 1938, 848). Steric and related factors, on the other hand, are known to influence both the energy of activation and the probability factor (A) or entropy of activation. The only comparable kinetic measurements on a series of polycyclic aromatic compounds which allow analysis of differences in activation energies and probability factors appear to be those reported in the present work. The total variation in rate constants is too small, however, to

provide a clear distinction as to the extent to which differences in E or A (both of which are almost within experimental uncertainty) contribute to variations in k. Nevertheless, since earlier work on the effects of benzenoid and other substituents (cf. Part VI, *J.*, 1947, 1096) and unpublished work on the effects of heterocyclic substituents has shown that differences in k were mainly due to differences in E, it will be assumed that the same applies in the polycyclic series. This assumption is supported by the work of Wibaut and Sixma (*loc. cit.*), according to which the differences in the rates of bromination of naphthalene in the 1- and the 2-position are almost entirely due to differences in E. It therefore appears justified, in the subsequent discussion, to employ differences in reaction rates directly as a measure of the electronic effects of substituents.

As previously (cf. Part VI, *loc. cit.*), we adopt Ingold's convention (*Chem. Reviews*, 1934, **15**, 233) of inductive (I) and tautomeric (T) effects, negative signs referring to electron-attraction and positive signs to electron-donation. The tautomeric effect falls into two parts, the permanent mesomeric (M) effect present in the ground state, and the additional electronic (E) effect, which represents a time-variable polarisability contribution operative in reacting molecules and reaches its maximum in the transition state. The time-variable counterpart of the inductive effect, the inductomeric effect, is likely to be small and is neglected. On this basis, the effect of a phenyl substituent is described as $-I,\pm T$. The $-I$ effect arises from the fact that the constituent atoms of a phenyl substituent, like those of any covalently unsaturated group, have less than their normal share of bonding electrons (the double-bond or π-electrons being less "bonding" than the single-bond or σ-electrons). The $-I$ effect would be expected to increase with increasing unsaturation in the sequence vinyl < phenyl < naphthyl < anthryl, phenanthryl, but to be much less than proportional to the number of double bonds in the substituent, since the additional unsaturation will be further and further removed from one particular point, and since the I effect, being mainly electrostatic in origin, rapidly decreases in the distance. The $\pm T$ effect of a phenyl substituent arises from the fact that it can partake of resonance forms of the type  and that the polarity will be mainly determined by X. Since the number of possible polar forms increases in the sequence phenyl < 2-naphthyl < 1-naphthyl < 9-phenanthryl < 9-anthryl, the $\pm T$ effects would be expected to increase in that order. The actual reactivity sequence will depend on a combination of the I and T effects. In a reaction facilitated by electron-recession, the $-I$ and $-T$ effects will reinforce each other and the expected reactivity sequence is the same as for the T effects. In a reaction requiring electron-accession on the other hand, the $-I$ and $+T$ effects will oppose each other and the actual sequence will depend on the relative magnitudes of the two effects. These may vary from case to case, as with other $-I,+T$ substituents, such as the halogens. Whatever the resultant sequence, the reactivity differences will be smaller than with a reaction requiring electron-recession.

An estimate of the I effects alone may be derived from the dissociation constants of the arylcarboxylic acids, arylamines, and aryl-hydroxy-derivatives, if it is assumed that the $+T$ and $-T$ effects brought into play by the forward and backward reactions are of equal magnitude, so that the equilibria will be determined only by the $-I$ effects. (Detailed consideration shows that this assumption is likely to be only approximately correct.) The available data (Table IV) bear out the expected sequence of $-I$ effects, vinyl < phenyl < 2-naphthyl < 1-napthtyl < phenanthryl < anthryl. (In assessing the differences quantitatively, it must be remembered that the $-I$ effects will exert opposite effects on the rates of the forward and backward reactions, and that the effect will be magnified in the dissociation constant, which is the ratio of the two.)

TABLE IV.

Dissociation constants of aryl derivatives.

X.	X·CO_2H (in water) ($\times 10^5$).	X·CO_2H (in 60% aqueous acetone) ($\times 10^5$).	X·OH ($\times 10^{10}$).	X·NH_2 ($\times 10^{10}$).
(Vinyl)	5·5 [1]	—	—	—
Phenyl	6·3 [1]	2·6 [4]	1·3 [5]	3·82 [6]
2-Naphthyl	6·8 [2]	2·8 [4]	2·5 [4]	1·29 [6]
1-Naphthyl	20·3 [2]	—	—	0·84 [6]
9-Anthryl	22·6 [3]	9·0 [4]	—	—
9-Phenanthryl	—	3·7 [4]	—	—

[1] Dippy, *Chem. Reviews*, 1939, **25**, 206. [2] Derick and Kamm, *J. Amer. Chem. Soc.*, 1917, **39**, 304. [3] Lauder, *Ber.*, 1937, **70**, 1288. [4] This paper (see Experimental). [5] Eisenbrand, *Z. physikal. Chem.*, 1929, *A*, **144**, 441. [6] Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.

An estimate of the differences in M effects should be obtainable from dipole moments, since these will be determined by the sum of the $-I$ and $\pm M$ effects. From a careful consideration of the moments of 1- and 2-chloronaphthalene, Hampson and Weissberger (*J.*, 1936, 393; cf. Ketelaar and Oosterhout, *Rec. Trav. chim.*, 1946, **65**, 448) deduced that there is a greater mesomeric effect in the 1- than in the 2-naphthyl derivative, but in general the interpretation of dipole moments in polycyclic derivatives is highly complicated owing to vectorial factors (cf. Bergmann and Hershberg, *loc. cit.*; Vassiliev and Syrkin, *Acta Physicochim.*, 1941, **14**, 414).

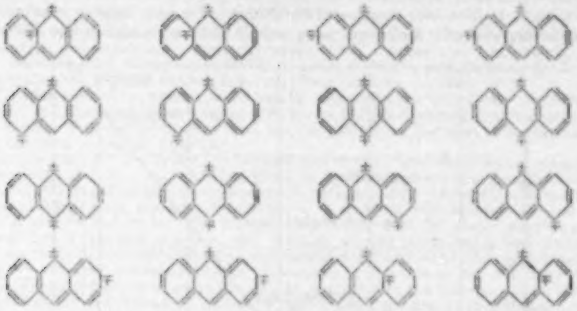
Turning again to the reactivity data in Table III, we see that the estimated differences in the rates of electrophilic substitution of the parent hydrocarbons are considerable and follow the expected sequence of $+T$ effects. In this case, therefore, the latter appear completely to outweigh the $-I$ effects. Amongst the side-chain reactions, the oxotropic rearrangement of the 1-aryl-3-methylallyl alcohols and the neutral hydrolysis of the arylmethyl bromides are facilitated by electron accession (type A; Ingold and Rothstein, *J.*, 1928, 1217), while the prototropic rearrangement of the 1-phenyl-3-arylmethyleneazomethines and the alkaline hydrolysis of the methyl naphthoates require electron recession (type B). As far as can be judged, all four reactions display the expected sequence vinyl < phenyl < 2-naphthyl < 1-naphthyl < 9-anthryl, showing that for these derivatives the $+T$ again outweigh the $-I$ effects in type A reactions. In each case, the differences in rate constants for the different aryl derivatives are remarkably small, in relation both to the effects of other substituents and to nuclear substitution. Thus, oxotropic rearrangement is known to be highly sensitive to substituent effects, *p*-methyl and *p*-methoxyl substituents attached to a phenyl group producing approximately 10- and 100-fold increases in rate, respectively (Braude and Stern, *J.*, 1947, 1096), yet a 9-anthryl as compared with a phenyl substituent only results in an approximately 5-fold increase, and the effects of the other polycyclic substituents studied are even smaller. The same applies to the other side-chain reactions, with the exception of the ammonolysis of aryl acetates where special factors are believed to be involved. The smaller reactivity differences in the side-chain as compared with the nuclear reactions may be due to the fact that, whereas the M effect must necessarily be the same in both types, the additional E effect may be much less prominent in the former than in the latter, as first suggested, in a different connection, by Bird and Ingold (*J.*, 1938, 918). This suggestion is also borne out by comparative data for a *p*-methyl substituent attached to a phenyl group; whereas in oxotropy the rate increase is about 10-fold, it is about 25-fold in nuclear nitration (Benford and Ingold, *J.*, 1938, 929) and about 400-fold in nuclear halogenation (Robertson, Johnston, and De La Mare, *loc. cit.*; Berliner and Bondhus, *J. Amer. Chem. Soc.*, 1946, **68**, 2355; 1948, **70**, 854).

In both side-chain oxotropy and side-chain prototropy, the rates of reaction of the 9-phenanthryl derivatives are unexpectedly small. This is unlikely to be due to any steric effect, since this should be even more pronounced with the 9-anthryl derivative, whereas the reactivity of the latter shows a quantitative linear correlation with the phenyl and naphthyl derivatives (see below), despite the fact that ultra-violet light absorption properties indicate that steric inhibition of resonance occurs in the rearranged isomer (Braude, Fawcett, and Newman, preceding paper). It is of course possible that steric hindrance plays a part in determining the side-chain reactivity of all the polycyclic derivatives, but nevertheless it does not readily explain the *relatively* low reactivity of the 9-phenanthryl derivatives, which therefore appears to be truly electronic in origin. If this deduction be correct, it can have only one explanation, namely, that the M effect of the phenanthryl group is unexpectedly small, smaller than that of the naphthyl and, probably, the phenyl group. In nuclear reactions, where the additional E effect is brought into play, this will not be apparent, but in side-chain reactions, where the E effect is weak, this will result in low reactivity; in type A reactions the $-I$ effect will not be sufficiently compensated by the $+M$ effect, and in type B reactions, the $-I$ effect will not be sufficiently enhanced by the $-M$ effect. The reason for the supposed abnormally small $\pm M$ effect of the phenanthryl group is not clear; it may be due to the two-directional polarisation consequent upon the " angular " arrangement of the benzene nuclei.

(3) *Quantitative Theory.*—(a) *Valence-bond method.* A simple approach to a quantitative or semi-quantitative theory of reactivity in polycyclic systems was outlined by Pauling (" The Nature of the Chemical Bond," Cornell, 1940), who pointed out that the reactivities of naphthalene in the 1- and the 2-position can be dicussed in terms of the respective numbers (n) of possible self-polarised structures; 7 self-polarised structures may be written containing a formal charge in the 1-position, and only 6 structures with a formal charge in the 2-position. This treatment can readily be extended to the comparison of the reactivities of different systems; thus $n = 3$

for a phenyl group, $n = 16$ for a 9-anthryl group and $n = 13$ for a 9-phenanthryl group. The 16 structures for a 9-anthryl group are shown below.

Self-polarised resonance structures of anthracene with a formal charge in the 9-position.

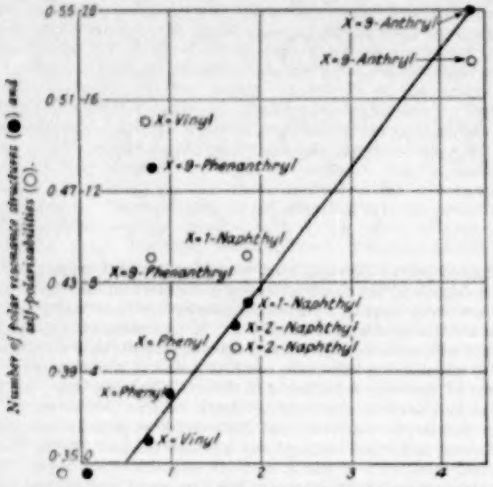


In the unsubstituted parent hydrocarbons, contributions from resonance forms of opposite polarity cancel each other, and the electron density is the same on each carbon atom; but under the influence of an attacking reagent, a particular polarity will be favoured and the polarisability or electromeric effect will be greater, the larger is n. In a substituted hydrocarbon, on the other hand, the substituent will result in a permanent mesomeric polarisation (which appears to be of prime importance in determining side-chain reactivity) and it is reasonable to suppose that, in comparing the effect of the same substituent in different hydrocarbons, the magnitude of the mesomeric effects, as well as of the electromeric effects, will run parallel to n. The quantitative correlation between heterolytic reactivity and the number of possible self-polarised structures depends on the following additional assumptions, amongst others: (1) The contributions of the different self-polarised structures of one system are approximately equal; (2) the excess (or deficiency in) electron-density is proportional to the number of contributing structures carrying a formal charge at a given point; (3) in side-chain reactions the resonance polarisation (mesomeric effect) outweighs any inductive effects. The figure shows a plot of the rate constants for the oxotropic rearrangements of the 1-aryl-3-methylallyl alcohols against n; a straight line is obtained except for the 9-phenanthryl derivative. The value for the corresponding vinyl derivative, 1-vinyl-3-methylallyl alcohol is included for comparison, and falls accurately on the linear plot. On the whole, therefore, the simple valency-bond resonance treatment is very successful in the present case, but it indicates an abnormally small M effect for the 9-phenanthryl group, a conclusion already reached from qualitative considerations. Probably assumptions (1) and (2) do not hold in this case.

A different type of valency-bond treatment, which takes into account contributions from excited (Dewar) structures containing ineffective bonds, has recently been developed by a number of workers (Svartholm, *Arkiv Kemi, Min. Geol.*, 1942, **15**, *A*, 1; Daudel and Pullman, *J. Phys. Radium*, 1946, **7**, 59, 74, 105; Pullman, *Experientia*, 1946, **2**, *A*, 364; Daudel and Daudel, *J. Chem. Physics*, 1948, **16**, 639). The contributions of Dewar-type structures are thought to be considerable, and the density of spin-paired, but ineffectively bonded, π-electrons is expressed as a "*charge totale* or free valency number" (Q), which should be a measure of heterolytic reactivity. The soundness of the underlying mathematical principles has been criticised by Moffitt (*Trans. Faraday Soc.*, 1949, **45**, 373), who calculates a different parameter, the "residual affinity" (r) which is a measure of the initial ease of displacement of an electron on a particular atom (Table V). Both Q and r run parallel, as they theoretically must, to the number n, of self-polarised structures, but the plots of k against Q or r are not linear. The scanty kinetic data so far available, therefore, indicate that contributions from polar structures are more important than contributions from Dewar structures, but further experimental evidence is clearly required on this point.

(*b*) *Molecular-orbital method.* A more elaborate approach to a quantitative theory of reactivity was initiated by Wheland and Pauling (*J. Amer. Chem. Soc.*, 1935, **57**, 2086) and has recently been greatly developed by Coulson and Longuet-Higgins (*Trans. Faraday Soc.*, 1947,

43, 87; *Proc. Roy. Soc.*, 1947, *A*, **191**, 39; **192**, 16; *Sci. J. Roy. Coll. Sci.*, 1948, **18**, 13; *J.*, 1949, 971). Here the electron densities are calculated by the method of molecular orbitals, assuming that the only forces acting on the π-electrons are the exchange forces between paired electrons and the Coulomb fields of the constituent atoms. In unsubstituted aromatic hydrocarbons, the π-electron densities on each carbon atom are unity, but heterolytic reactivity is expressed by the self-polarisabilities (χ) which are a measure of the change in electron density (expressed in terms of the resonance intergral β of a π-electron pair) produced by a change in the electrostatic field.



Relative rates of anotropic rearrangement of X·CH(OH)·CH:CHMe.

Pauling and Wheland calculated χ for benzene and naphthalene and obtained the values 0·40 (benzene), 0·40 (naphthalene, 1-position) and 0·44 (naphthalene, 2-position). The results of the more refined and extensive calculations of Coulson and Longuet-Higgins are shown in Table V.

TABLE V.

Theoretical quantities related to heterolytic reactivity.

	Number of polar resonance structures (*n*).	"Charge totale." (*Q*).[1]	"Self-polarisabilities" (χ).[2]	"Residual affinities" (*r*).[2]
(Vinyl)	1	—	0·500	—
Phenyl	3	0·073	0·398	−0·246
2-Naphthyl	6	0·097	0·405	−0·220
1-Naphthyl	7	0·123	0·443	−0·206
9-Phenanthryl	13	—	0·442	—
9-Anthryl	20	0·25	0·526	−0·174

[1] Daudel and Daudel, *J. Chem. Physics*, 1948, **16**, 639. [2] Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, **192**, *A*, 16; *J.*, 1949, 971; Longuet-Higgins, *Sci. J. Roy. Coll. Sci.*, 1948, **18**, 13. [3] Moffitt, *Trans. Faraday Soc.*, 1949, **45**, 373.

It will be seen that χ again runs parallel, as it theoretically must, to the number *n* of simple self-polarised structures, but the quantitative relationships are somewhat different for the two parameters. Thus, whereas the values of *n* indicate, in agreement with experiment, that the difference in heterolytic reactivity between benzene and naphthalene should be greater than the difference in reactivity between the 1- and the 2-position in naphthalene, the values of χ predict the reverse relationship. Again, it seems reasonable to suppose that the polarisability not only of the parent hydrocarbons under the influence of a reagent, but also of the permanent polarisation of a series of hydrocarbon derivatives carrying the same substituent should be directly

related to χ. The figure shows that the plot of the rate constants for the oxotropic rearrangements of the 1-aryl-3-methylallyl alcohols against χ departs considerably more from the linear, however, than the plot of k against n. As before, the value of k for the phenanthryl derivative shows a particularly large deviation.

Experimental.

Materials.—The carbinols are described in the preceding paper. The aryl carboxylic acids for dissociation-constant measurements were crystallised from ethanol and had the m. p.s given in parentheses: benzoic (121°), 2-naphthoic (184°), 9-anthroic (217°), and 9-phenanthroic acid (256°). Dioxan and acetone were purified as previously described (Brande, *J.*, 1948, 1971).

Kinetic Measurements.—The technique of kinetic measurements previously described has been further simplified and improved by employing a Beckman DU photoelectric spectrophotometer for the spectrometric assay. This undoubtedly renders the method one of the most convenient and accurate for measuring the rates of organic reactions.

The appropriate amount (10—50 mg.) of carbinol was weighed into a short glass capsule, moistened with one or two drops of dioxan, and added to 25 ml. of reaction medium contained in a special reaction vessel (Part V, *loc. cit.*) immersed in a thermostatically controlled bath. At suitable time intervals, 1 ml. of solution was withdrawn and immediately diluted to 10 or 50 ml. with absolute ethanol and 1 ml. of 0·01N-aqueous potassium hydroxide. The intensity of absorption of the diluted solution at the chosen wave-length was then determined in a 1-cm. cell, the same solvent being used in the comparison cell.

Normally, one of the maxima exhibited by the rearranged carbinol was chosen for intensity determinations. A slightly different procedure had to be adopted in the case of the 9-anthryl derivative, as solutions of the rearranged carbinol are so strongly fluorescent that the maxima do not obey the Beer–Lambert law even at low extinctions (cf. Brande, Fawcett, and Timmons, *J.*, in the press); moreover, the differences in intensities of the maxima of the two isomers are in any case rather small. It was possible, however, to find empirically a wave-length (2650 A.) on a part of the curve at which the intensity was directly proportional to the concentration of rearrangement product and good first-order rate constants were obtained in this way.

Rearrangements of X·CH(OH)·CH:CHMe *in aqueous dioxan–0·01N-hydrochloric acid at* 30°.

c_{ROH} = carbinol concentration (% w/v); c_d = dioxan concentration (% v/v).

(I) X = 1-Naphthyl, c_{ROH} = 0·197, c_d = 60.

Time (mins.)	0	15·0	20·0	25·0	30·0	35·0	420	
$E^{1\%}_{1\,cm.}$ (at 2960 A.)	119	248	279	303	326	345	440	
10^4k (min.$^{-1}$)	—	345	344	341	346	347	—	(Mean) 345

(II) X = 1-Naphthyl, c_{ROH} = 0·192, c_d = 80.

Time (mins.)	0	28·0	45·1	65·0	85·1	106·0	1080	
$E^{1\%}_{1\,cm.}$ (at 2960 A.)	119	221	268	307	340	360	451	
10^4k (min.$^{-1}$)	—	132	132	129	129	123	—	(Mean) 129

(III) X = 2-Naphthyl, c_{ROH} = 0·0365, c_d = 60.

Time (mins.)	0	15·0	23·0	30·2	37·0	45·0	720	
$E^{1\%}_{1\,cm.}$ (at 2455 A.)	123	1040	1410	1640	1855	2010	2600	
10^4k (min.$^{-1}$)	—	310	317	318	323	319	—	(Mean) 318

(IV) X = 2-Naphthyl, c_{ROH} = 0·0360, c_d = 80.

Time (mins.)	0	20·0	40·0	60·0	80·2	100·	1080	
$E^{1\%}_{1\,cm.}$ (at 2455 A.)	123	704	1140	1465	1710	1970	2650	
10^4k (min.$^{-1}$)	—	132	128	125	123	129	—	(Mean) 127

(V) X = 9-Anthryl, c_{ROH} = 0·0371, c_d = 60.

Time (mins.)	0	6·1	8·0	10·5	11·5	13·0	100	
$E^{1\%}_{1\,cm.}$ (at 2650 A.)	165	230	246	255	269	281	336	
10^4k (min.$^{-1}$)	—	780	800	785	815	820	—	(Mean) 800

(VI) X = 9-Anthryl, c_{ROH} = 0·0372, c_d = 80.

Time (mins.)	0	10·0	15·0	20·0	26·0	31·0	420	
$E^{1\%}_{1\,cm.}$ (at 2650 A.)	165	207	224	242	255	268	325	
10^4k (min.$^{-1}$)	—	308	308	329	318	321	—	(Mean) 316

(VII) X = 9-Phenanthryl, c_{ROH} = 0·191, c_d = 60.

Time (mins.)	0	20·0	28·0	36·1	45·0	55·0	720	
$E^{1\%}_{1\,cm.}$ (at 3030 A.)	62	174	213	250	277	301	504	
10^4k (min.$^{-1}$)	—	146	149	153	148	147	—	(Mean) 148

(VIII) X = 9-Phenanthryl, c_{ROH} = 0·185, c_d = 80.

Time (mins.)	0	50·0	70·1	90·0	110	130	1080	
$E^{1\%}_{1\,cm.}$ (at 3030 A.)	62	190	230	265	295	321	511	
10^4k (min.$^{-1}$)	—	67·1	66·0	66·1	66·0	66·1	—	(Mean) 66·3

The rate constants were calculated from the expression $k = 2{\cdot}3 \log[(a - x_0)/(a - x)]/t$, where t = time in minutes, x_0 = initial intensity, x = intensity at time t, and a = final intensity at the wave-length chosen. The final intensities a were identical within experimental error (±2%) with the intensities at the same wave-lengths of the pure rearranged carbinols. Some typical runs are reproduced above. The majority of the k values given in Table I are averaged from several runs.

Energies of activation ($E_{Ass.}$) were computed graphically from the plots of rate constants against $1/T$. The plots were satisfactorily linear. Probability factors refer to specific rate constants (k/c_A) and were calculated from the expression $\log A = 0{\cdot}722E_{Ass.} + \log(k_{Ass.}/c_A) - 1{\cdot}78$, where c_A = acid concentration = 0·01M.

Determination of Dissociation Constants.—The dissociation constants of the aryl carboxylic acids were determined spectrophotometrically in 60% (by vol.) aqueous acetone, bromophenol-blue being used as indicator. (For the general principles of colorimetric and spectrometric acidity measurements, see Brode, *J. Amer. Chem. Soc.*, 1924, **46**, 581; Braude, *J.*, 1948, 1971; Stock and Davies, *J.*, 1949, 1371.) High accuracy was not essential for the present purpose and a simple procedure was adopted in which the hydrogen-ion concentration of suitable carboxylic acid solutions was determined by direct interpolation of the indicator ratios with those of dilute hydrogen chloride solutions. Since the commercial bromophenol-blue employed is not a pure substance and also since it is somewhat unstable in solution, absorption intensities are not recorded in absolute units, but as extinctions (E) of neutral and acid solutions of identical indicator concentrations (*ca.* 0·02%). E values were determined at the maximum (5850 A.) in a 1-cm. cell, a Beckman DU photoelectric spectrophotometer being used. In the following table, E_B refers to the neutral solutions and E_A to the acid solutions, c is the acid concentration in g.-mols./l., and I is the indicator ratio given by $(E_B - E_A)/E_A$.

Acid.	$10^3\,c$.	E_B.	E_A.	I.	$10^3\,[H^+]$.	f.	$10^4\,K_A$.
HCl	0·4	0·715	0·450	0·59	4	—	—
,,	0·6	0·715	0·195	2·7	6	—	—
,,	0·8	0·715	0·121	4·9	8	—	—
,,	1·0	0·715	0·082	7·7	10	—	—
Benzoic	19	1·449	0·330	3·4	6·6	0·90	2·0
2-Naphthoic	10·9	1·449	0·413	2·5	5·8	0·92	2·8
9-Anthroic	5·7	1·463	0·294	3·95	7·1	0·94	9·0
9-Phenanthroic	9·4	1·449	0·364	3·0	6·2	0·92	3·7

On plotting the acid concentration c against I for the hydrochloric acid solutions, a straight line is obtained in the range $I = 0{\cdot}5$—$5{\cdot}0$ which is also that of highest accuracy in I (Braude, *loc. cit.*). Since hydrogen chloride is almost completely dissociated in 60% aqueous acetone (cf. Braude and Stern, *J.*, 1948, 1978), and since the ionic-strength correction (Stock and Davies, *loc. cit.*) is negligible at the low acid concentrations employed, c_{HCl} can be equated to the hydrogen-ion concentration $[H^+]$. The hydrogen-ion concentration of the carboxylic acid solutions could then be evaluated directly from the I–$[H^+]$ plot. The data show that, under the conditions chosen, the carboxylic acids are all less than 15% dissociated and the dissociation constants K_A are given by $K_A = f^2[H^+]^2/(c - [H^+])$. The activity coefficients f were calculated from the expression $\log f = -1{\cdot}1\sqrt{c}$, based on the limiting Debye–Hückel equation which should be sufficiently applicable at the low ionic strengths involved. The dielectric constant of 60% aqueous acetone at 25° was taken as 48 (Akerlöf, *J. Amer. Chem. Soc.*, 1932, **54**, 4125).

We thank the Department of Scientific and Industrial Research for a Maintenance Grant to one of us (J. S. F.).

Imperial College of Science and Technology,
London, S.W.7.

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160. *The Kinetics of Aromatic Halogen Substitution. Part VII. Nitrosobenzene and Azobenzene.*

By P. W. Robertson, T. R. Hitchings, and G. M. Will.

The reaction between bromine and nitrosobenzene in carbon tetrachloride shows a period of induction, and in the presence of hydrogen bromide proceeds at a rate 10^{10} times as fast as the bromination of benzene under the same conditions. Hydrogen bromide is consumed in the process, and is also found to react with nitrosobenzene in carbon tetrachloride by a very fast reaction. A mechanism is proposed involving, as the first stage, the formation of the compound PhNBr·OH, which after rearrangement further reacts with bromine to form the various products. Azobenzene gives a measurable reaction with bromine in acetic acid at 35° only in the presence of hydrogen bromide, and here also the first stage appears to involve the preliminary addition of hydrogen bromide. Water decelerates this reaction to an unmeasurable rate in 20% aqueous acetic acid, and in the same mixed solvent chlorine reacts with azobenzene at a slow rate, five times as fast as with benzene.

Nitrosobenzene on bromination in carbon disulphide readily forms *p*-bromonitrosobenzene to the extent of as much as 40%, together with other compounds, of which *pp'*-dibromoazoxy-

benzene is present in the greatest amount (Ingold, *J.*, 1925, 513); likewise in benzene solution there is rapid formation of *p*-bromonitrosobenzene (Le Fèvre, *J.*, 1931, 810). This easy *para*-bromination of nitrosobenzene is unexpected, as the nitroso-group, although it can exert a $+T$ effect, has $-T$, $-I$ characteristics also; its dipole moment (3·2 D., directed away from the benzene ring) is greater than that of a *tert.*-alkyl nitroso-compound, a condition that usually determines *meta*-substitution and a slow rate of reaction. It has been suggested that the reaction taking place is the bromination of a dimer (Hammick *et al.*, *J.*, 1934, 29). We find from light-absorption measurements that there is very little difference in the intensity of colour of solutions of nitrosobenzene in acetic acid (in which the solute is unimolecular), carbon disulphide, and carbon tetrachloride, over the concentration range, M/40—M/160, at 16°. It seems probable that the concentration of the dimer in these solutions is too small to cause the rapid reactions that are observed, even if it should have a constitution favourable for *op*-substitution.

Nitrosobenzene reacts with bromine in carbon tetrachloride at a variable rate, and on examination of the solutions in a dim light a period of induction may sometimes be observed, the start of the reaction being indicated by a cloudiness spreading through the liquid. With added hydrogen bromide, there is no period of induction, and the reaction becomes moderately reproducible, a reaction mixture containing nitrosobenzene (M/80), bromine, (M/80), and hydrogen bromide (M/400) having a half-reaction time of three minutes at 17°; rising bimolecular coefficients indicate the autocatalytic nature of the process.

% bromine absorption (x)	20	30	40	50	60	70
k_2 (min.$^{-1}$ g.-mol.$^{-1}$ l.)	20	23	25	27	30	35

In these experiments, the reaction was stopped by shaking the solution with aqueous potassium iodide, and it was established that iodine which entered the organic phase during the titration was not acting as a catalyst, though the opposite is usually found for bromination in carbon tetrachloride.

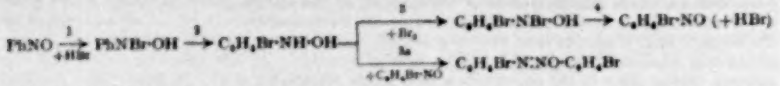
It is instructive to compare the rates of bromination of nitrosobenzene and mesitylene. The latter has been shown to halogenate about 10^8 times faster than benzene (*J.*, 1943, 276), and therefore about 10^9 times faster than chlorobenzene (*J.*, 1948, 100). Catalysis by hydrobromic acid of its bromination (reactants, M/40, in carbon tetrachloride at 25°) results in only a threefold increase of rate with M/10-catalyst, the initial rate under these conditions being given by $k_2(x = 10) = 0{\cdot}3$. Thus nitrosobenzene, which brominates only slowly in the absence of a catalyst, reacts with bromine some 100 times as rapidly as mesitylene (and hence perhaps 10^{10} times as rapidly as benzene), when hydrobromic acid is added, despite the expected deactivation of the aromatic ring by the nitroso-group. These facts indicate that the bromination of nitrosobenzene proceeds by some mechanism other than that of normal electrophilic substitution. An atom-chain mechanism appears to be excluded as the rate of reaction is insensitive to light, and is the same in a nitrogen atmosphere as in the presence of air, the oxygen of which might oxidise the hydrogen bromide and initiate chains.

In another series of experiments in carbon tetrachloride the rates were measured by stopping the reaction with a dilute solution of sodium peroxide, and titrating the bromide ion produced. Part of the total bromine could not be accounted for, owing to the fact that some of the bromine of the hydrogen bromide formed had entered the benzene ring. The reaction, measured in this way, was found to proceed at a similar fast rate, and with M/80- (and also M/40-) reactants the disappearance of hydrogen bromide amounted to about 45% of that which should have been produced by substitution.

The reaction between nitrosobenzene and hydrogen bromide was examined kinetically. With M/80-reactants in carbon tetrachloride at 17°, the reaction proceeded rapidly to 50% absorption (0·7 minute), and stopped with about 70% absorption of the hydrogen bromide. The products of this reaction were found by Bamberger *et al.* (*Ber.*, 1899, **32**, 210) to be *p*-bromophenylhydroxylamine, *pp'*-dibromoazoxybenzene, *p*-bromoaniline, and 2 : 4-dibromoaniline. As *p*-bromophenylhydroxylamine is an intermediate product, we have also studied the reaction between phenylhydroxylamine and bromine. With M/40-reactants in carbon tetrachloride at 17°, 80% of the bromine was absorbed in about 0·7 minute, and a further 5% more slowly. The products of this reaction included a dark, slightly soluble material, and *p*-bromonitrosobenzene.

The results of these various rate-measurements, and the experiments by Ingold and by Bamberger, provide evidence for establishing a probable mechanism for the bromination of

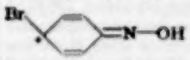
nitrosobenzene. The reaction begins by the addition of hydrogen bromide to the nitrosobenzene, and then proceeds as now indicated, all the changes being rapid ones.



Stage 2 in this scheme is analogous to the conversion of *N*-bromoacetanilide into the *p*-bromo-derivative; stages 3 and 4 are to be expected as a similar change takes place on the bromination of phenylhydroxylamine, and stage 3a takes place by condensation of the *p*-bromophenylhydroxylamine with *p*-bromonitrosobenzene. An alternative side-reaction proceeding to a limited degree appears to be, $C_6H_4Br{\cdot}NH{\cdot}OH \longrightarrow C_6H_3Br(OH){\cdot}NH_2 \longrightarrow C_6H_3Br(OH){\cdot}N{:}N{\cdot}C_6H_4Br$, as we have found that on treating the reaction product with aqueous alkali a yellow solution is obtained. This is consistent with the intermediate formation of *p*-bromophenylhydroxylamine, as its change to 4-bromo-2-hydroxyphenylhydroxylamine is known to take place.

With equimolecular amounts of nitrosobenzene and bromine about 10% of the bromine remains unconsumed, and since about 45 molecules % of hydrogen bromide are used in proceeding by route 3a, about one quarter of the total bromine must take part in the formation of more highly substituted products. As, according to Bamberger, *p*-bromoaniline is produced by the action of hydrogen bromide on nitrosobenzene, this would be brominated to form tribromoaniline. Another change requiring more bromine is, $C_6H_4Br{\cdot}NBr{\cdot}OH \longrightarrow C_6H_3Br_2{\cdot}NH{\cdot}OH \longrightarrow C_6H_3Br_2{\cdot}NO{\cdot}N{\cdot}C_6H_4Br$, and tribromoazoxybenzene has been identified as a product (Hammick *et al.*, *loc. cit.*).

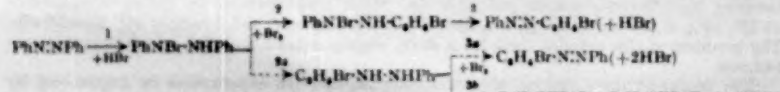
The reactivity of the bromine in *p*-bromonitrosobenzene has been discussed in connexion with the anomalous bromination of nitrosobenzene. This bromo-compound reacts with silver nitrate in acetic acid solution not only more rapidly than *p*-bromonitrobenzene but even more rapidly than picryl bromide (Le Fèvre, *loc. cit.*). Here also a reaction involving initial addition to the nitroso-group is not excluded, or it may be possible that the reactive molecule is



Azobenzene, on monobromination in acetic acid, forms *p*-bromoazobenzene (Janovsky and Erb, *Ber.*, 1886, **19**, 2156; 1887, **20**, 357; Burns, McCombie, and Scarborough, *J.*, 1928, 2928). We have now made a kinetic study of this reaction. A freshly prepared solution of M/40-bromine in acetic acid did not react with M/40-azobenzene (at 35°) during 16 hours. If this bromine solution is kept a fortnight or illuminated for several hours (both of which procedures have been found to cause the formation of a small amount of hydrogen bromide), or if hydrogen bromide is added, the reaction then proceeds. In the presence of sodium acetate or water, the reaction is inhibited. The bromination of azobenzene can be examined only with small amounts of hydrogen bromide, as this causes the formation of an insoluble salt, $PhN{:}NPh,HBr_3$, and for this same reason the reaction can be followed kinetically only during the initial stages under the selected experimental conditions. The rates determined with M/40-azobenzene and M/40-bromine at 35°, in acetic acid solution which contained (*ca.* M/1000-) hydrogen bromide and varying amounts of added water, are:

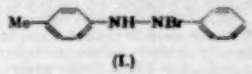
H_2O (%)	0	10	25
k_2 ($x = 5$)	0·05	0·0040	~0

The effect of water on normal electrophilic substitution is to cause a considerable increase in the rate of reaction. It is evident that in the bromination of azobenzene a special mechanism operates involving the participation of hydrogen bromide. It was further found that hydrogen bromide very slowly added to azobenzene, giving a product in which the bromine no longer reacted with silver nitrate. It is therefore proposed that the first stage in the bromination of azobenzene proceeds by the addition of hydrogen bromide:

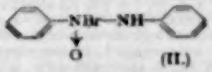


As the bromination of azobenzene is very considerably faster than its reaction with hydrogen bromide, the change is considered to proceed chiefly by stages 2 and 3. Route 2a appears to be followed to some extent, however, and it is possible that tetrabromobenzidine, identified as a product by Mills (*J.*, 1894, 54), arises in this way, *via* a benzidine change and subsequent bromination (route 3b).

The theory involving the prior addition of hydrogen bromide in the bromination of azobenzene explains also the behaviour of related compounds. Under the conditions in which azobenzene is brominated, *p*-methylazobenzene does not react (Burns *et al.*, *loc. cit.*); the difference in the electronegativity of the nitrogen atoms in this compound causes the formation of the addition product (I), which, according to the scheme proposed, is unreactive, since the position *para*- to the amino-group is blocked.



(I.)

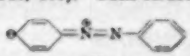


(II.)

Azoxybenzene, which, like azobenzene, reacts with bromine in acetic acid only in the presence of hydrogen bromide, would give preferably the addition compound (II) and this would be substituted in the benzene ring not attached to the NO group, as is found experimentally.

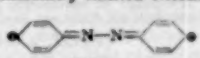
The chlorination of azobenzene, like its bromination, does not proceed with a freshly prepared solution of chlorine in acetic acid, but only when hydrogen chloride is present. Water added to the acetic acid solution causes the rate to increase towards the true electrophilic rate. Such a reaction was not observed with bromine because the substitution is slower by several powers of ten than chlorination, and becomes unmeasurable. The rate of chlorination of azobenzene in 20% aqueous acetic acid at 25° ($k_2 = 0{\cdot}055$) is about five times that for benzene ($k_2 = 0{\cdot}012$) under the same conditions.

Although azobenzene, like nitrosobenzene, has lone pairs of electrons on the nitrogen atoms capable of conjugation with the aromatic ring (structures III, IV, V), such conjugation appears not to be favoured, since the C–N and N–N bond lengths in azomethane and azobenzene are almost identical (Brockway, *Rev. Modern Physics*, 1936, **8**, 231; Hampson and Robertson, *J.*, 1941, 409). Such structures apparently contribute to an extremely limited extent to the



(III.)

(IV.)



(V.)

polarisability of the molecule, since it has now been shown that azobenzene reacts with chlorine only a little faster than benzene, and, correspondingly, the apparently fast bromination of nitrosobenzene involves a special mechanism. The relative unreactivity of these compounds to electrophilic halogenation should be contrasted with the great reactivity of acetanilide and aniline; the former compound brominates about as rapidly as mesitylene (Part I, *J.*, 1943, 276), and therefore some 10^9 times faster than benzene.

Experimental.

The nitrosobenzene was prepared as required and was kept in a refrigerator before use; the different samples melted at 67°.

Typical rate measurements of bromine absorption are: N/80-PhNO + N/80-Br_2 + N/400-HBr; 8 ml. in CCl_4 at 17°; 20 ml. of KI + 20 ml. of N/80-$Na_2S_2O_3$ added; 8 ml. of this aqueous solution titrated with N/200-I_2.

Time (mins.)	0	2	5	10	12	1	3	6·5	8
Titre (ml.; average)	2·0	4·2	7·8	8·7	9·0	3·25	5·6	8·7	9·1
Bromine absorption (%)	0	27	73	84	88	15	45	83	89

These values give a smooth curve, as did other values obtained in experiments under nitrogen and under air.

A rate measurement in which bromine and hydrogen bromide were determined gave the following results:

N/80-PhNO + N/80-Br_2 + N/400-HBr; 8 ml. in CCl_4 at 17°; 10 ml. of dilute Na_2O_2 soln. were added, and 4 ml. of aqueous soln. were removed, acidified with acetic acid, and titrated with N/20-$AgNO_3$ (eosin):

Time (mins.)	0	1	2	4	6	10	20
Titre (ml.; average)	3·44	2·78	2·50	1·78	1·46	1·28	1·16
Br_2 + HBr absorption (%)	0	42	60	106	127	139	147

Other runs gave similar results, and the average of 10 runs, with reaction times 20 to 60 minutes, showed 145% absorption.

M/40-PhNO + M/40-HBr; 8 ml. in CCl_4 at 17°; titrations as in the experiment just described :

Time (mins.)	0	3	7	29
Titre (ml.)	3·1	1·2	1·1	0·9
HBr absorption (%)	0	61	65	70

M/40-PhNH·OH + M/40-Br_2; in CCl_4 at 17°.

Time (mins.)	0·7	2	8
Bromine absorption (%)	84	87	87

Azobenzene, m. p. 66—67°, and azoxybenzene, m. p. 34—35°, were used for the following measurements : M/40-Azobenzene + M/40-Br_2 + approximately M/1000-HBr at 35° in acetic acid; $x = 5$, $t = 42$; $x = 10$, $t = 100$ (at about $x = 10\%$ absorption of bromine, solid began to be deposited); in acetic acid containing 10% water, $x = 5$, $t = 500$. Other measurements, with bromine and an unknown amount of hydrobromic acid, similarly showed slower rates in aqueous than in glacial acetic acid, and also were subject to considerable retardation by added sodium acetate. M/40-Azoxybenzene + M/40-Br_2 + approximately M/1000-HBr; $x = 5$, $t = 100$. Both water and sodium acetate also reduced the rate of bromination of this compound. M/40-Azobenzene + M/40-Cl_2 in acetic acid containing 20% water at 25°, $x = 10$, $t = 80$.

The relative absorption by nitrosobenzene in different solvents was compared by use of a photoelectric colorimeter, for the red light of a mercury-vapour lamp. The following percentage transmissions were recorded at 16° : M/40-solution, in CCl_4, 38; in acetic acid, 36; in CS_2, 37; M/80-solution, in CCl_4, 52·5; in acetic acid, 52·5; in CS_2, 53·5.

Victoria University College,
Wellington, New Zealand.

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161. *The Kinetics of Halogen Substitution. Part VIII. Halogen Addition. Part XV. Benzyl and Allyl Chloride, Bromide, and Cyanide.*

By L. D. Swindale, B. E. Swedlund, and P. W. Robertson.

The order of reactivity, per molecule, is PhH > Ph·CH_2Cl > Ph·CH_2Br > Ph·CH_2·CN for chlorine substitution, and

$$CH_2{:}CH_2 \gg CH_2{:}CH{\cdot}CH_2Cl > CH_2{:}CH{\cdot}CH_2Br > CH_2{:}CH{\cdot}CH_2{\cdot}CN$$

for bromine addition. The theories relating to these reactions are discussed.

The rates of aromatic substitution, as well as the orientation of the products, are of importance in elucidating the mechanisms involved in the process. This has been demonstrated by Ingold and his co-workers for nitration by the competitive method (*J.*, 1938, 905, 918, 929), and for chlorination, in the present series of investigations, for alkylbenzenes and halogenonaphthalenes (*J.*, 1943, 279; 1948, 100). The benzyl halides and in general compounds of the type Ph·CH_2X may also be investigated by this method. Whilst the present work was in progress there appeared a paper by Ingold and Shaw (*J.*, 1949, 575) on the relative rates of nitration of benzyl chloride and ethyl phenylacetate.

Our preliminary rate measurements of the chlorination of benzyl chloride in acetic acid solution showed variations greater than might be accounted for by experimental error. It was found further that in the presence of mercuric chloride these rates were lowered, whereas mercuric chloride accelerated the chlorination of toluene under the same conditions. The conclusion was that in the relatively very slow reaction with benzyl chloride nuclear substitution was accompanied by an atom-chain reaction involving side-chain substitution, and that the mercuric chloride acted as a chain-breaker. It was also ascertained that in the mixed solvent, 20% aqueous acetic acid, which would be expected to eliminate the chain-reaction, the ratio of the toluene and benzyl chloride rates was the same as in acetic acid containing mercuric chloride. The use of such a mixed solvent for the determination of comparative rates involves the risk, for benzyl chloride and bromide, of concomitant hydrolysis with the formation of a more reactive compound. No autocatalysis, however, could be detected in the chlorination of benzyl chloride, and in particular the per cent. absorption–time curves for benzene and benzyl chloride remained proportionate throughout the experimental range. Another possible disturbance is that in the benzyl bromide reaction there might be simultaneous substitution of bromine by chlorine. Such a reaction would be expected to proceed with acceleration, but

here also there was no evidence of autocatalysis. It is known, moreover, that replacements of this type tend to take place more especially when there is considerable electron-accession to the point of attack, *e.g.*, in a compound such as *p*-Me·C_6H_4·CH_2Br.

Herewith are the relative initial rates of chlorination, in 20% water–acetic acid at 25°, of benzene and the compounds, Ph·CH_2X.

PhH	Ph·CH_2Cl	Ph·CH_2Br	Ph·CH_2·CN
1	0·76	0·61	0·17

Accurate percentages of *o*-, *p*-, and *m*-substitution products are known for nitration, but not for chlorination of some of the compounds examined. The values for *m*-nitration are for Ph·CH_2Cl (15%), Ph·CH_2Br (7%), and Ph·CH_2·CN (14%), and it is not to be expected that there should be a large difference for chlorination. At all events the reactions are proceeding chiefly to give *p*,*o*-chloro-compounds, and the relative rates in the foregoing table are substantially those for substitution in these positions. The relative rate of nitration of benzene to that of benzyl chloride, molecule per molecule, found by Ingold and Shaw (*loc. cit.*) was 1 : 0·302, indicating that benzyl chloride is more deactivated on nitration than on chlorination. In nitration the reagent is the ion NO_2^+, and in chlorination the chlorine molecule, and benzyl chloride with its permanent dipole is likely to hinder the approach of the positive ion more than the neutral molecule. A similar difference in reactivities was found between nitration and halogenation for aromatic compounds containing halogen in the nucleus (*J.*, 1948, 104).

Attention is now turned to the relative rates of chlorination of the three compounds Ph·CH_2X. Chlorine has a greater inductive effect than bromine, but the difference between the dipole moments of Ph·CH_2Cl (1·85 D.) and Ph·CH_2Br (1·86 D.) is inconsiderable. In benzyl chloride the carbon atoms in the ring should be somewhat more deactivated than in benzyl bromide, and the superior reactivity of the chloride is consequently caused by the greater hyperconjugation of the hydrogen atoms in the chloromethyl group. Benzyl cyanide, on the other hand, has a greater dipole moment (3·52 D.), so that in this compound the deactivation must be more considerable than in the benzyl halides. The rate of chlorination, however, is not greatly inferior, so the hyperconjugation effect here must be large. This involves the weakening of the C–H bond by the CN group, and in this connection it is known that benzyl cyanide forms a sodium salt, Ph·CHNa·CN.

If groups such as chloromethyl act in aromatic substitution by a hyperconjugation effect reduced by an opposing inductive effect, they may be expected to act in a similar manner in causing halogen addition to ethylene compounds. The previously measured rates of bromine addition to the allyl halides in acetic acid solution are now compared with that of allyl cyanide, the velocities being calculated as second order coefficients at 25° for reactants at M/80 (x = 10% absorption):

CH_2:CH·CH_2Cl	CH_2:CH·CH_2Br	CH_2:CH·CH_2·CN
k_2 = 1·6	k_2 = 1·1	k_2 = 0·23

In our earlier communication (*J.*, 1945, 131) the rate order, allyl chloride > allyl bromide, was considered to be anomalous, and it was suggested that it might have been caused by intervention of solvent molecules in the reaction; but the same rate ratio is found, not only in acetic acid and aqueous acetic acid solutions, but also for the reactions in the polar aprotic solvent chlorobenzene. In the non-polar carbon tetrachloride these rates appear to be reversed (Juvala, *Ber.*, 1930, **63**, 1998), but we find it difficult to obtain reproducible results for these compounds in this solvent, even in an atmosphere of dry nitrogen.

The allyl cyanide reaction in acetic acid solution is autocatalytic like those of the bromide and chloride owing to the formation of hydrogen bromide caused by the participation of solvent molecules. The following third order coefficients for bromine addition to allyl cyanide, reactants M/80, in acetic acid at 25°, show this effect.

x, %	10	20	30	40	50	60
k_3	20	23	28	33	40	53

Correspondingly, the reaction is largely catalysed by the lithium halides, as is seen from the initial rates, now calculated as second order coefficients:

	No catalyst.	LiCl, M/20.	LiBr, M/20.
$k_2(x = 10)$	0·23	2·4	1·2

Thus for allyl cyanide, like other compounds of the type CHR′:CH_2, where R′ is a group with $+T,-I$ characteristics, LiCl is superior to LiBr as a catalyst, and as the $-I$ effect (measured by the dipole moment) is large, the catalysis is considerable (cf. *J.*, 1949, 294).

The rate of bromine addition to ethylene has now been determined by a revised technique, specially applicable to volatile reactants, and this will be described in a later communication. These measurements have, for reasons of solubility, been made in a mixed solvent composed of chloroform and carbon tetrachloride, and the rate of bromine addition to allyl bromide was measured in the same solvent. On combining these results with those shown above for the reactions in acetic acid, the following relative rates are obtained :

$CH_2{:}CH_2$	$CH_2{:}CH{\cdot}CH_2Cl$	$CH_2{:}CH{\cdot}CH_2Br$	$CH_2{:}CH{\cdot}CH_2{\cdot}CN$
1	0·019	0·013	0·0027

A comparison of this series with the one obtained for the chlorination of the benzyl compounds reveals that the order of reactivity is the same, but with a different deactivation effect in the two series. These results are consistent with the operation of a mechanism with similar electron requirements in the two reactions; but the deactivation by the CH_2X group is more considerable in the allyl compounds, where the dipole is nearer to the point of attack. The same effect has been observed for the compounds PhBr and $CH_2{:}CHBr$, since the bromine atom has the same $+T, -I$ characteristics as the CH_2X groups at present being investigated.

Just as in the compounds $Ph{\cdot}CH_2X$, there is the possibility of either *o*-, *p*-, or *m*-substitution, so also in the allyl compounds two modes of reaction, (I) and (II), are possible. According to

(I.) $CH_2{=}CH{-}CH_2{-}Cl$ (II.) $CH_2{=}CH{-}CH_2{-}Cl$

(I), hyperconjugation operates, whilst in (II) the mechanism is dependent on the inductive effect of the CH_2Cl group, reinforced by halogen-hyperconjugation. Certainly, Kharasch has shown that hydrogen iodide and normal hydrogen bromide addition to the allyl bromide takes place entirely by method (I); but other reagents that add to the double link may behave differently. In the case of bromine addition an approximate estimate may be made of the relative contributions of the two reactions. From a consideration of the velocities of halogen addition to $CHPh{:}CH{\cdot}CO_2H$ and $CH_2{:}CH{\cdot}CO_2H$, the same ratio of velocities being assumed for $CHPh{=}CH{\cdot}CH_2Cl$ and allyl chloride reacting as $CH_2{=}CH{\cdot}CH_2Cl$, bromine addition proceeding by method (II) would represent 12% of the total reaction. Although, therefore, bromine addition to the compounds $CH_2{:}CH{\cdot}CH_2X$ is directed chiefly by mechanism (I), just as in the compounds $Ph{\cdot}CH_2X$ halogen substitution is chiefly in the *p*,*o*-positions, there may also be an appreciable contribution from reaction by method (II).

Experimental.

The following compounds were used in the investigations: benzyl chloride, b. p. 178—178·5°/758 mm.; benzyl bromide, b. p. 195—197°/749 mm.; benzyl cyanide, b. p. 233—234°/760 mm.; benzene, m. p. 5°; allyl cyanide, b. p. 116—117°/753 mm.

The technique for the experiments was as previously described. Herewith is a typical bromine addition reaction :

M/80-Allyl cyanide + M/80-Br_2 in acetic acid at 25°; reaction mixture 10 ml.; 1-ml. samples titrated with KI and N/80-$Na_2S_2O_3$:

Time (mins.)	0	31·0	120	271	0	60·6	183	330
Titre (ml.)	1·99	1·86	1·39	0·88	1·99	1·67	1·16	0·79

From combined graph, $x = 10\%$, $t = 37$ mins.

Other measurements in acetic acid at 25° are: M/80-allyl cyanide + M/80-Br_2; (i) + M/20-LiCl, $x = 10$, $t = 3{\cdot}74$; (ii) + M/20-LiBr, $t = 7{\cdot}2$. In 10% aqueous acetic acid at 0°, M/80-allyl chloride + M/80-Br_2, $x = 50$, $t = 5{\cdot}4$; M/80-allyl bromide + M/80-Br_2, $x = 50$, $t = 8{\cdot}4$. In chlorobenzene at 25°, M/40-allyl chloride + M/40-Br_2, $x = 20$, $t = 76$; M/40-allyl bromide + M/40-Br_2, $x = 20$, $t = 112$.

Herewith is a typical chlorine-substitution reaction : M/2-Benzyl bromide + M/20-Cl_2 in 20% aqueous acetic acid at 25°; reaction mixture 10 ml.; 2-ml. samples titrated with KI + N/10-$Na_2S_2O_3$.

Time (mins.)	0	20·7	54·1	0	30·0	45·1	0	75·0
Titre (ml.)	1·98	1·77	1·50	1·95	1·66	1·50	1·97	1·42
Blank (ml.)	1·96	1·91	1·86	1·94	1·89	1·83	1·98	1·92

From combined graph, $x = 10\%$, $t = 25{\cdot}7$ mins.

Other results (expressed in minutes) in 20% aqueous acetic acid at 25°: M/2-Benzene + M/20-Cl_2, $x = 10$, $t = 15{\cdot}5$; M/2-benzyl chloride, + M/20-Cl_2, $x = 10$, $t = 20{\cdot}4$; M/2-benzyl cyanide + M/20-Cl_2, $x = 10$, $t = 92{\cdot}1$.

Victoria University College, Wellington, New Zealand. [*Received, December 6th*, 1949.]

162. *Aryl-2-halogenoalkylamines. Part VI. Reactions with Certain Organic Sulphur Compounds.*

By W. C. J. Ross.

The reaction of *NN*-di-2-chloroethyl-*p*-anisidine with 2-mercaptoethanol and thiophenol in aqueous alcohol solutions of different pH has been studied. Thioethers react with arylhalogenoalkylamines to give sulphonium compounds. 4-Aryl-substituted thiazans are conveniently prepared by the reaction of aryl-di-2-halogenoalkylamines and sodium sulphide in aqueous acetone.

THE reactivity of the carcinogenic and tumour-growth inhibitory arylhalogenoalkylamines towards various anions and amines was discussed in Parts III and IV (*J.*, 1949, 2589, 2824) of this series. In the present communciation some reactions of the halogenoalkylamines with certain organic sulphur compounds are described.

It has already been established in Part III that the carbonium ion derived from an " aromatic nitrogen mustard " could not react with an undissociated carboxyl group and it was thought that reaction with an undissociated thiol group was also improbable. To test this point it was necessary to allow the arylhalogenoalkylamines to react in solutions of different pH containing thiols of known dissociation constants. Since it had been found previously that aqueous acetone solutions could not be used for the quantitative study because of mercaptal formation it was necessary to determine the pK of typical thiols in aqueous alcoholic solution. Thiophenol and 2-mercaptoethanol were chosen as representative of aromatic and aliphatic thiols and found to have pK_a 8·05 and 10·8, respectively, in 50% alcohol.

Table I shows the results obtained when *NN*-di-2-chloroethyl-*p*-anisidine reacted with these thiols in solutions of varying pH. Under the experimental conditions all the halide will react and there is 100% excess over the amount required to react with the added thiol.

TABLE I.

Reaction of NN-*di-2-chloroethyl*-p-*anisidine in 50% ethanol with thiophenol and 2-mercaptoethanol. Concn. of amine* 0·01M. *Concn. of thiol* 0·01M. *Temp.* 85°. *Time* 30 *mins.*

Added salts.	pH change during reaction.	PhSH, % reacted.	$CH_2(SH)\cdot CH_2\cdot OH$, % reacted.
Nil	4·0—2·3	nil	nil
0·01M-HOAc + 0·01M-NaOAc	6·3—6·0	—	10
0·05M-NaOAc	8·6—6·6	90	33
0·20M-Na_2HPO_4	9·6—8·8	—	75
0·05M-Na_2CO_3	11·0—10·8	97	98

It is not easy to make experiments of this type very precise because in order to control the pH of the solution during the reaction various salts have to be added and the anions derived from each type will have characteristic competition factors towards the carbonium ions. The pH values, measured with a glass electrode, are only apparent values but as the pKs of the thiols were measured under identical conditions an estimate of the amount of thiol in the dissociated form can be made. Notwithstanding the imperfections of the method it is clear that the reaction with thiols is dependent on pH. In acid solutions where dissociation is suppressed there is no reaction but as the pH rises more thiol will ionise and as was expected more reaction occurs.

The results also indicate that a negatively charged sulphur atom is a powerful nucleophilic centre having a great affinity for the carbonium ion, since Table I shows considerable reaction with mercaptoethanol under conditions where only a small proportion of the thiol group will be dissociated. If this small fraction reacts rapidly with the halide then more will dissociate and eventually appreciable reaction will occur. A number of compounds which have high competition factors for carbonium ions, for example, dithiophosphates, mono- and di-thiophosphonates, thiosulphate, and dithiocarbamate (Ogston, *Trans. Faraday Soc.*, 1948, **44**, 45), are highly dissociated in solution giving ions containing, in effect, negatively charged sulphur atoms.

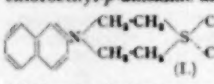
If only the dissociated form of a thiol can react then the competition factor for any thiol at a given pH should be $f \times F_{s^-}$, where f is the fraction of the thiol in the ionic form—an activity coefficient—and F_{s^-} is the competition factor of the ion. Some idea of the order of the competition factor of a negatively charged sulphur atom can be obtained from Ogston's figures for mustard gas. The competition factor of cysteine at pH 7 is given as $1{\cdot}2 \times 10^5$ and since

cysteine has $pK_a = 10{\cdot}5$ the value of f will be about $10^{-3{\cdot}5}$ at pH 7·0. The value of the competition factor F_{S^-} of the ionised sulph-hydryl group will be $1{\cdot}2 \times 10^3/10^{-3{\cdot}5}$ or about 4×10^6. It is interesting to note that the value of the competition factor for dithiophosphate at pH 7—when f will be approximately unity—is of the same order, namely $1{\cdot}3 \times 10^6$. This high value may be compared with the values for organic-acid anions which range from 20 to 100.

Quite generally, the competition factor of a compound at any pH will be given by the expression $f_a \times F_A$ where f_a is the fraction of the substance in the reactive form at pH $= n$, which can be calculated from the dissociation constant, and F_A is the competition factor of the reactive form A—this will be the anion for an acid or a thiol and the free base for an amine.

In a mixed biological system at physiological pH—usually about 7·5—the extent to which any substance will react with the carbonium ion derived from an " aromatic nitrogen mustard " will be proportional to $f_{7{\cdot}5} \times F_A \times c$ where c is the concentration of the substance being considered. When an arylhalogenoalkylamine is administered to an animal in the relatively low dosage required to inhibit tumour growth or to induce tumour formation, in the affected cells a small amount of reagent is distributed amongst a large excess of reacting groups. It is clear that the various substances present will react in proportion to the value of the expression given above. As the mustard-gas type of compound is not an efficient inhibitor of so-called ·SH enzymes (compare Dixon and Needham, *Nature*, **1946**, **158**, 432) despite the high value of F_{S^-} one must conclude that the value of c for the ·SH group in the tissues involved is low. Another factor is that the ·SH groups in proteins are situated on the relatively short cysteine side-chains and may not be as accessible for reaction as the more exposed carboxy- and amino-groupings. Consideration of the factors mentioned above suggests that the groups most likely to react are the acid groups of proteins and the phosphoryl and aromatic type amino-groups in nucleic acids.

The isolation of *NN*-di-2-phenylthioethyl-*p*-anisidine from the reaction between *NN*-di-2-chloroethyl-*p*-anisidine and thiophenol in alkaline aqueous acetone solution at 66° was described in Part IV; the same product is obtained when the reaction is carried out at 37° and the β-*naphthyl* derivative has now been prepared in a similar manner from β-naphthyldi-2-chloroethylamine. No crystalline product has been isolated from the reaction between *NN*-di-2-chloroethyl-*p*-anisidine and mercaptoethanol but when sodium picrate is added to the product of the reaction between β-naphthyldi-2-chloroethylamine and this thiol a small quantity of the *picrate* (I) of a thiazan derivative is obtained. In Part IV it was shown that when the chlorine atom on one side-chain of an aryldihalogenoalkylamine was replaced by ·NHR the rate of ionisation of the second chlorine atom was increased. It was of interest to discover the effect of replacing the first chlorine atom by ·SR. Unfortunately it was not possible to ascertain this effect in as direct a way as that used in the case of the amines since the reaction has to be carried out in the presence of a buffer salt and the total halide reacting cannot be determined directly in the presence of the thiol. Table II shows the results obtained when *NN*-di-2-chloroethyl-*p*-anisidine reacted under various conditions in 50% acetone: an excess of thiol is present in this experiment so that the small loss by mercaptal formation is not significant.



(I.)

TABLE II.

Reaction of NN-*di-2-chloroethyl-*p*-anisidine in* (a) 50% *acetone*; (b) 50% *acetone containing sodium acetate* (0·20M.); (c) *and* (d) *as* (b) *but also containing thiophenol* (0·04M.). *Concn. of amine*, 0·01M. *Temp.* 66°. *Time:* (a), (b), *and* (c), 30 *mins.*, (d) 2 *hours.*

	(*a*).	(*b*).	(*c*).	(*d*).*
H^+, %	58	6·8	76	95
Cl^-, %	58	79·5	—	—

* No extra acidity was developed if this solution was heated for a longer period, hence all the halide had reacted.

Column (*d*) indicates that the carbonium ion derived from the arylhalogenoalkylamine reacts with the thiol—and possibly to a small extent with water—and the acetate anion in the ratio 95 : 5. If one makes the reasonable assumption that thiol and acetate react in the same ratio in (*c*) then the total extent of carbonium-ion formation can be shown to be 80% in 30 minutes. It was shown in Part III that the amount of chloride ion produced when a dihalide reacted in the presence of 0·2M-sodium acetate closely represented the actual extent of the formation of the carbonium ion. Column (*b*) indicates that under the conditions chosen,

78·5% of the dihalide ionises; this is practically identical with the extent of ionisation in the presence of thiol. It can therefore be concluded that the replacement of the first chlorine atom in an aryldi(halogenoalkyl)amine by ·SR does not significantly affect the rate at which the second chlorine atom ionises.

The possible formation of sulphonium compounds by the reaction of halogenoalkylamines with thioethers is of interest because of the natural occurrence of such ethers, *e.g.* methionine. When *NN*-di-2-chloroethyl-*p*-anisidine reacts at 66° in aqueous acetone containing an excess of phenyl methyl sulphide titration of the liberated hydrogen and chloride ions indicates that about 9% of the halide has formed a sulphonium salt, the reaction of the halide with the thioether giving chloride ion but no hydrogen ion :

$$NR_2{\cdot}CH_2{\cdot}CH_2Cl \longrightarrow \underset{+\,Cl^-}{NR_2{\cdot}CH_2{\cdot}\overset{+}{C}H_2} + R'SR'' \longrightarrow NR_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}\begin{matrix}R'\\ \diagup\\ \diagdown\\ R''\end{matrix}$$

Approximately the same proportion of β-naphthyldi-2-chloroethylamine reacts to form sulphonium salt at 37°. In the presence of dibutyl sulphide the *p*-anisidine derivative reacts to give 26% of the sulphonium salt. The readier formation of sulphonium halides from dialkyl sulphides than from aryl alkyl sulphides has already been noted (cf. Hickinbottom, "Reaction of Organic Compounds," London, 1940, p. 114). The formation of the thiazan derivative (I) involves internal sulphonium salt formation in the monosubstitution product.

Good yields of aryl-substituted thiazans are obtained when aryldi-2-halogenoalkylamines are heated with aqueous acetone solutions of sodium sulphide. The method appears to be of general application and is a very convenient one for the preparation of such thiazans as 4-phenyl-, 4-m- and 4-p-*tolyl*-, 4-p-*chlorophenyl*-, 4-p-*methoxyphenyl*-, and β-*naphthyl-thiazan*.

There is some discrepancy in the literature concerning the properties of 4-phenylthiazan. Helfrich and Reid (*J. Amer. Chem. Soc.*, 1920, **42**, 1208, quoted in Heilbron and Bunbury's "Dictionary of Organic Compounds," London, 1943) obtained a compound, m. p. 108—111°, by the action of 2-dichloroethyl sulphide on aniline in the cold whilst Okáč (*Chem. Listy*, 1934, **28**, 227) obtained an oil when the same reactants were heated under reflux with sodium acetate and sodium carbonate in ethanol solution. Korshak and Strepikheev (*J. Gen. Chem. Russia*, 1944, **14**, 312) prepared the thiazan as a solid, m. p. 32·3—32·6°, by heating *NN*-di-2-chloroethylaniline with sodium sulphide in absolute alcohol and Cerkovnikov and Stern (*Archiv Kem.*, 1946, **18**, 12) obtained the same product by a similar method using *NN*-di-2-bromoethylaniline hydrobromide. The present results are in agreement with the findings of the Russian workers.

Experimental.

Determination of the pK_a *of Thiophenol and 2-Mercaptoethanol.*—2-Mercaptoethanol (780 mg.) or thiophenol (1·10 g.) was dissolved in aqueous ethanol (200 ml.; 50% by volume) and titrated with potassium hydroxide solution (0·82N. in 50% ethanol). The pH of the solution was measured after each addition of alkali by use of a glass-electrode system with a Cambridge portable electrometer valve pH meter. The results for 2-mercaptoethanol were :

ml. of KOH.	% neutralisation.	pH.	pK_a.	ml. of KOH.	% neutralisation.	pH.	pK_a.
0	0	7·1	—	7·5	53	10·8	10·8
1·5	11	9·9	10·8	9·0	63	11·0	10·8
3·0	21	10·2	10·8	10·5	74	11·4	10·9
4·5	31	10·4	10·8	12·0	84	12·0	—
6·0	42	10·6	10·7				

The average pK_a value of 2-mercaptoethanol in 50% ethanol is 10·8 and the corresponding value for thiophenol is 8·05.

Reaction of NN-Di-2-chloroethyl-p-anisidine with Mercaptoethanol and Thiophenol in 50% Ethanol.—*NN*-Di-2-chloroethyl-*p*-anisidine (500 mg.), contained in a small specimen tube, was added to boiling aqueous ethanol (200 ml.; equal volumes) containing either mercaptoethanol (156 mg.) or thiophenol (200 mg.), and the mixture was heated under reflux for 30 minutes. (A thermometer in the boiling liquid registered 85°.) The cooled solution was diluted with an equal volume of water and, after the addition of glacial acetic acid (1 ml.), the amount of unreacted thiol present was determined by titration with 0·1N-iodine (starch indicator). The experiment was repeated with various salts present; Table I shows the proportion of thiol reacting under different conditions. The pH of the solution was measured before and after the reaction on a parallel run using the method alread described.

Reaction of β-Naphthyldi-2-chloroethylamine with Thiophenol.—β-Naphthyldi-2-chloroethylamine (500 mg.), thiophenol (0·5 ml.), and sodium hydroxide (5 ml.; N.) were dissolved in aqueous acetone (500 ml.; 50%) and kept at 37° for 4 days. During this time the solution became turbid and oily droplets separated. After removal of the acetone under reduced pressure the product was extracted with benzene, and the dried extract was passed through a column of activated alumina. The eluates

contained *β-naphthyldi-(2-phenylthioethyl)amine* which crystallised from benzene–light petroleum (b. p. 60—80°) as prisms, m. p. 113—114° (Found: C, 74·9; H, 6·2. $C_{44}H_{39}NS_4$ requires C, 75·2; H, 6·1%).

Reaction of β-Naphthyldi-2-chloroethylamine with 2-Mercaptoethanol.—Naphthyldi-2-chloroethylamine (1·4 g.), mercaptoethanol (3 ml.), sodium hydroxide (25 ml.; N.), and 50% acetone (500 ml.) were heated under reflux for 5 hours. Removal of the acetone yielded an oil which was dissolved in aqueous methanol containing picric acid and sodium picrate. After several days a small quantity of *picrate* had separated from the solution; it recrystallised from acetone–methanol as rhombs, m. p. 200° (decomp.) (Found: C, 52·6; H, 4·2; N, 11·6. $C_{28}H_{23}O_8N_5S$ requires C, 52·6; H, 4·4; N, 11·2%).

Reaction of NN-Di-2-chloroethyl-p-anisidine with Thiophenol in 50% Acetone Solution at 66°.—*NN*-Di-(2-chloroethyl)-*p*-anisidine (500 mg.), dissolved in 50% acetone (200 ml.) (*a*) alone, (*b*) containing crystalline sodium acetate (5·44 g.), or (*c*) containing thiophenol (880 mg.) and sodium acetate (5·44 g.), was heated under reflux for 30 minutes. The cooled mixture was titrated first with 0·1N-sodium hydroxide (phenolphthalein indicator) and then, after the addition of glacial acetic acid (1 ml.), with 0·1N-iodine (starch indicator). The difference between these titres represents the amount of acid produced by the reaction of the arylhalogenoalkylamine. The results are shown in Table II.

Reaction of NN-Di-2-chloroethyl-p-anisidine and β-Naphthyldi-2-chloroethylamine with Thioethers in 50% Acetone Solution at 66°.—*NN*-Di-2-chloroethyl-*p*-anisidine (500 mg.), dissolved in 50% acetone (200 ml.) containing (*a*) phenyl methyl sulphide (620 mg.) or (*b*) dibutyl sulphide (730 mg.), was heated at 66° for 30 minutes. Titration of the hydrogen ion and chloride ion indicated (*a*) H, 52·5; Cl, 57·5%; thus 5/57·5 or 8·8% of the halide reacting formed a sulphonium salt, and (*b*) H, 43·0; Cl, 54·0%; *i.e.* 15/58 or 26% of the halide yielded a sulphonium compound.

When β-naphthyldi-2-chloroethylamine (536 mg.) was dissolved in 50% acetone (400 ml.) containing phenyl methyl sulphide (620 mg.) and the solution kept at 37° for 24 hours titration indicated H, 18·5; Cl, 20·5%: the amount of halide converted into sulphonium salt being 2/20·5 or 9·8%.

Preparation of 4-Arylthiazans.—*NN*-Di-2-chloroethyl-*p*-anisidine (1 g., 4 millimols.) and sodium sulphide (5 g.) dissolved in 50% acetone (200 ml.) were heated under reflux for 2 hours. The solid which separated from the cooled mixture after removal of the acetone under reduced pressure was crystallised from light petroleum (b. p. 40—60°). 4-*p*-*Methoxyphenylthiazan* was obtained as long prismatic needles, m. p. 76—77° (Found: C, 63·1; H, 7·3. $C_{11}H_{15}ONS$ requires C, 63·1; H, 7·2%). Other thiazans were obtained by a similar procedure except that longer times of reaction were required for the more slowly reacting arylhalogenoalkylamines (*e.g.*, 15 hours were allowed for the reaction with *p*-chloro-*NN*-di-2-chloroethylaniline). The following have been prepared: 4-Phenylthiazan, m. p. 31°; picrate, m. p. 141° (Korshak and Strepikheev, *loc. cit.*, give m. p. 141—142°). 4-*m*-Tolylthiazan, an oil which gives a *picrate* (prisms from acetone–methanol), m. p. 187—188° (Found: C, 48·7; H, 4·4. $C_{17}H_{18}O_7N_4S$ requires C, 48·4; H, 4·3%). 4-*p*-*Tolylthiazan* [prisms from light petroleum (b. p. 40—60°)], m. p. 33—35° (Found: C, 68·4; H, 8·0. $C_{11}H_{15}NS$ requires C, 68·4; H, 7·8%); *picrate* (large plates from acetone), m. p. 155° after sintering at 143° and resolidifying (Found: C, 48·7; H, 4·5%). 4-*p*-*Chlorophenylthiazan* [prisms from light petroleum (b. p. 40—60°)], m. p. 70—71° (Found: C, 56·2; H, 5·7. $C_{10}H_{12}NCIS$ requires C, 56·2; H, 5·7%). 4-*β*-*Naphthylthiazan* [prisms from light petroleum (b. p. 60—80°)], m. p. 82—83° (Found: C, 73·1; H, 6·7. $C_{14}H_{15}NS$ requires C, 73·2; H, 6·6%)

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THE CHESTER BEATTY RESEARCH INSTITUTE,
FULHAM ROAD, LONDON, S.W.3.

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163. *Some 1:7- and 1:2:7-Derivatives of Naphthalene.*

By HERBERT H. HODGSON and RAYMOND E. DEAN.

7-Bromo-1- and 8-bromo-2-naphthylamine, 1-bromo-7- and 7-bromo-1-nitronaphthalene, 1:7-dibromonaphthalene, the 2-halogeno-1:7-dinitronaphthalenes, and 7-nitronaphthalene-2:1-diazo-oxide, and the nitration of 7-nitro-*m*-nitrobenzenesulphon-2-naphthalide are described. The nitration of 1:7-dinitro-*m*-nitrobenzenesulphon-2-naphthalide occurs in the naphthalene nucleus as shown by hydrolysis of the nitration product to 1:5(?):7-trinitro-2-naphthylamine. The last compound does not form a picrate or deaminate readily.

1:7-DINITRO-2-NAPHTHYLAMINE is readily diazotised by Hodgson and Walker's method (*J.*, 1933, 1620), and 2-chloro-, 2-bromo-, and 2-iodo-1:7-dinitronaphthalene are obtained by subsequent Sandmeyer reactions. Special conditions are necessary for the preparation of 7-nitronaphthalene-2:1-diazo-oxide.

Nitration of 1:7-dinitro-*m*-nitrobenzenesulphon-2-naphthalide occurs in the naphthalene nucleus and not in the side chain, as is shown by hydrolysis of the trinitrated product to a 1:*x*:7-trinitro-2-naphthylamine, where *x* has not been determined but on all analogy should be the 5-position. 1:5(?):7-Trinitro-2-naphthylamine would not form a picrate, owing either

to steric or more probably to the much enfeebled basic character of the 2-amino-group. Similarly, 1 : 7-dinitro-2-naphthylamine is inert towards *m*-nitrobenzenesulphonyl chloride. Attempts to deaminate the trinitro-compound by the cuprous oxide–methanol procedure, described for 1 : 7-dinitro-2-naphthylamine, were unsuccessful.

Experimental.

Improvements in the Preparation of 2 : 7-*Dinitronaphthalene.*—Using a modification of Hodgson and Ward's method (*J.*, 1945, 590), 3 : 6-dinitronaphthalic anhydride (20 g.) is added during *ca.* 4 minutes to boiling dry quinoline (40 c.c.) containing copper bronze (5 g.) in suspension, and then more copper bronze (5 g.) is added and boiling continued for a total period of 15 minutes. Synthetic quinoline affords a cleaner product in somewhat better yield (34%) than does coal-tar quinoline (about 23%).

Preparation of Some 1 : 7-*Derivatives of Naphthalene.*—*8-Bromo-2-naphthylamine.* A solution of 1-bromo-7-nitro-2-naphthylamine (2·3 g.) (Hodgson and Ward, *J.*, 1947, 227) in sulphuric acid (5 c.c.; *d* 1·84) was added to one of sodium nitrite (1 g.) in sulphuric acid (5 c.c.; *d* 1·84), the whole was stirred into glacial acetic acid (20 c.c.) at <20°, and stirring was continued for 30 minutes. The mixture was then added gradually to a stirred suspension of cuprous oxide (4 g.) in methanol (70 c.c.) at 55°, and the stirring continued until the solution had cooled to room temperature, whereupon the whole was poured on ice and kept overnight. The precipitate was filtered off, washed with water, 2% aqueous sodium carbonate, and again with water, and then extracted with boiling ethanol (charcoal). The extract was filtered and allowed to evaporate, whereupon 1-*bromo*-7-*nitronaphthalene* separated (1·25 g., 58% yield); it recrystallised from ethanol in orange plates, m. p. 135° (Found: N, 5·7; Br, 31·6. $C_{10}H_5O_2NBr$ requires N, 5·5; Br, 31·7%). 1-Bromo-7-nitronaphthalene (1 g.) was reduced by being heated under reflux for 3 hours with a mixture of iron powder (pin dust) (3·0 g.), ferrous sulphate (0·5 g.), and water (30 c.c.); the solid was filtered off, washed with cold water, dried, and extracted with boiling ethanol (charcoal), and the filtered extract allowed to evaporate, whereupon 8-*bromo*-2-*naphthylamine* (0·4 g.) separated and was recrystallised from ethanol; it formed pale brown rods, m. p. 74° (Found: N, 6·5; Br, 35·9. $C_{10}H_8NBr$ requires N, 6·3; Br, 36·0%).

1 : 7-*Dibromonaphthalene.* A fine suspension of 7-*bromo*-1-*naphthylamine hydrobromide* [(Found: Br, 52·6. $C_{10}H_9NBr_2$ requires Br, 52·8%), obtained as colourless needles when 7-bromo-1-naphthylamine (2·0 g.) was dissolved in hot hydrobromic acid (2·5 c.c.; *d* 1·7) and water (15 c.c.), and the solution chilled to 0°] was diazotised at 0° by the addition of sodium nitrite (1 g.) in the minimum amount of water. After 20 minutes, the clear solution was stirred into one of cuprous bromide (4 g.) in hydrobromic acid (10 c.c.; *d* 1·7) at 60° and stirring continued until room temperature was attained; the mixture was poured on to ice and kept overnight. The latter was then filtered off, washed with water, 2% aqueous sodium carbonate, and finally with water, and extracted with boiling ethanol (charcoal). The extract was allowed to crystallise, and the crystals (0·15 g.) were recrystallised from ethanol, 1 : 7-*dibromonaphthalene* being obtained in colourless needles, m. p. 61° (Found: Br, 55·7. $C_{10}H_6Br_2$ requires Br, 55·9%).

7-Bromo-1-nitronaphthalene (5·7 g.) was obtained from 8-nitro-2-naphthylamine (10 g.) by the same procedure as above, and crystallised from ethanol in small pale yellow needles, m. p. 107° (Salkind and Filinov, *J. Gen. Chem. Russia*, 1934, **4**, 979, give m. p. 110—111°) which could not be raised by repeated crystallisation (Found: N, 5·6; Br, 31·5. Calc. for $C_{10}H_6O_2NBr$: N, 5·5; Br, 31·7%). *Brit. Abs.*, 1935, 204, incorrectly describe this compound as 2-bromo-7-nitronaphthalene.

7-*Bromo*-1-*naphthylamine.* Finely powdered 7-bromo-1-nitronaphthalene (4 g.) was heated under reflux for 3 hours with iron powder (pin dust) (12 g.), crystallised ferrous sulphate (2 g.), and water (100 c.c.), the mixture was filtered cold, and the residue washed with cold water, dried, and extracted with boiling ethanol. The extract, after being boiled with animal charcoal, was filtered, and the filtrate allowed to evaporate slowly, but crystallisation was unsatisfactory. The solid obtained was dissolved in hot 5% hydrochloric acid, and, from the cooling solution, 7-*bromo*-1-*naphthylamine hydrochloride* (3·2 g.) separated in white gleaming plates, m. p. 250° (Found: HCl, 14·0. $C_{10}H_8NBr,HCl$ requires HCl, 14·1%), which darkened on exposure to light. Basification with ammonia afforded pure 7-*bromo*-1-*naphthylamine* (2·8 g.), which crystallised from ethanol in colourless needles, m. p. 52° (Found: Br, 35·8. $C_{10}H_8NBr$ requires Br, 36·0%), that became mauve-brown in air.

Preparation of Some 1 : 2 : 7-*Derivatives of Naphthalene.*—*The* 2-*halogeno*-1 : 7-*dinitronaphthalenes.* 1 : 7-Dinitrotoluene-*p*-sulphon-2-naphthalide (2·3 g.; m. p. 171°; cf. Hodgson and Ward, *J.*, 1947, 1060, who give m. p. 165—166°) was hydrolysed by dissolution in sulphuric acid (5 c.c.; *d* 1·84) and heating at 40° for 5 minutes, a solution of sodium nitrite (1 g.) in sulphuric acid (5 c.c.; *d* 1·84) was added, and the mixture was stirred dropwise into glacial acetic acid (20 c.c.) at <20°. After a further 30 minutes' stirring the solution was divided into three equal portions which were dealt with separately as follows: (*a*) was stirred into a solution of cuprous chloride (2·5 g.) in hydrochloric acid (25 c.c.; *d* 1·18), and, when evolution of nitrogen had ceased, the thick dark mixture was poured into iced water, and the pale yellow precipitate (0·45 g.) was kept overnight, then filtered off, and washed with water (500 c.c.), 2% aqueous sodium carbonate (150 c.c.), and water (500 c.c.), dried at 70°, and extracted with boiling ethanol (charcoal); on evaporation, the filtered extract afforded 2-*chloro*-1 : 7-*dinitronaphthalene* (0·2 g.), which recrystallised from ethanol in pale brown needles, m. p. 161° (Found: Cl, 13·9. $C_{10}H_5O_4N_2Cl$ requires Cl, 14·0%); (*b*) was poured into a solution of cuprous bromide (2·5 g.) in hydrobromic acid (25 c.c. *d* 1·7), and then dealt with as in (*a*); the crude 2-*bromo*-1 : 7-*dinitronaphthalene* (0·6 g.) obtained crystallised from ethanol in yellow micro-needles (0·25 g.), m. p. 149° raised by sublimation to 155—156° (Found: Br, 27·0. $C_{10}H_5O_4N_2Br$ requires Br, 26·9%); (*c*) was stirred into a solution of potassium iodide (5 g.) in an amount of water insufficient for complete dissolution; the mixture was kept until reaction had ceased, then stirred into iced water and left overnight; the red precipitate (0·6 g.) was removed, washed with water (500 c.c.) and aqueous sodium thiosulphate (10 g. of solid in 500 c.c. of water), and dried at 70°; extraction as for (*a*) and (*b*) gave 2-*iodo*-1 : 7-*dinitronaphthalene*, which crystallised

from ethanol in reddish-fawn rods, m. p. 163°, which sublimed to very pale fawn needles, m. p. 166° (Found: I, 36·7. $C_{10}H_6O_2N_2I$ requires I, 36·69%).

7-*Nitronaphthalene*-2 : 1-*diazo-oxide*. When a solution of 1 : 7-dinitro-2-naphthylamine (0·5 g.) in sulphuric acid (4 c.c.; *d* 1·84) was treated at <10° with one of sodium nitrite (1 g.) in sulphuric acid (5 c.c.; *d* 1·84) and the mixture stirred into a suspension of copper carbonate (3 g.) in glacial acetic acid (25 c.c.) there was an immediate precipitation of 7-*nitronaphthalene*-2 : 1-*diazo-oxide* (0·45 g.), which was filtered off, washed three times with water (100 c.c.) and dried at 50°; it separated from ethanol in clusters of pale yellow sword-like crystals (Found: N, 19·8. $C_{10}H_5O_3N_3$ requires N, 19·5%) which darkened on exposure to light, decomposed at *ca.* 160°, and coupled with alkaline β-naphthol. When a solution of the above diazonium sulphate was stirred into glacial acetic acid (18 c.c.) at <20° and the mixture poured into iced water (300 c.c.), only slight precipitation occurred (0·05 g.).

7-*Nitro*-m-*nitrobenzenesulphon*-2-*naphthalide*. 7-Nitro-2-naphthylamine (6 g.) was intimately ground with m-nitrobenzenesulphonyl chloride (75 g.) and the mixture heated under reflux with pyridine (25 c.c.) for 3 hours. The solution was cooled to 0° and then stirred dropwise into 15% aqueous hydrochloric acid (200 c.c.); the precipitate of 7-nitro-m-nitrobenzenesulphon-2-naphthalide (9·1 g.) was filtered off, washed with water, sucked as dry as possible on the Büchner funnel, and crystallised twice from 70% acetic acid (charcoal). It was obtained in clusters of golden needles, m. p. 212—213° (Found: N, 11·4; S, 8·5. $C_{16}H_{11}O_6N_3S$ requires N, 11·2; S, 8·6%).

The Nitration of 7-*Nitro*-m-*nitrobenzenesulphon*-2-*naphthalide*.—(a) *With an equimolecular amount of nitric acid in glacial acetic acid*. The naphthalide (2 g.) was boiled with glacial acetic acid (15 c.c.), the mixture cooled to 50°, and a crystal of sodium nitrite added, followed by the dropwise addition, with stirring, of 2 c.c. of a solution of nitric acid (4·4 c.c.; *d* 1·5) in glacial acetic acid (35·6 c.c.). The temperature was then raised and kept at 80° for 5 minutes. 3 Hours later, glacial acetic acid (15 c.c.) was added at 15° with stirring, and next morning the suspension was filtered, and the solid 1 : 7-*dinitro*-m-*nitrobenzenesulphon*-2-*naphthalide* (1·7 g.) washed with glacial acetic acid and ether, and dried; it crystallised from glacial acetic acid (charcoal), in which it is sparingly soluble, in yellow micro-needles, m. p. 246—247° (decomp.) (Found: N, 13·3. S, 7·8. $C_{16}H_{10}O_8N_4S$ requires N, 13·4; S, 7·7%).

(b) *With 5-fold excess of nitric acid in glacial acetic acid*. With the same procedure as above but with 10 c.c. of nitrating reagent, the yield of 1 : 7-dinitro-m-nitrobenzenesulphon-2-naphthalide was practically unchanged (1·8 g.; m. p. 246—247°). Hydrolysis occurred when the naphthalide (1 g.) was stirred into sulphuric acid (50 c.c.; *d* 1·84) and slow dissolution completed by heating to 70°. The clear solution was kept overnight; it was filtered on to ice, and the 1 : 7-dinitro-2-naphthylamine which precipitated was crystallised from glacial acetic acid (charcoal); it formed golden yellow needles, m. p. and mixed m. p. with an authentic specimen, 248—249°.

(c) *With nitric acid* (d 1·5). The powdered naphthalide (2·8 g.) was added portionwise during 15 minutes to nitric acid (15 c.c.; *d* 1·5), initially below 5°, and the temperature not allowed to exceed 20°; it was raised to 35° when complete dissolution had occurred. After 3 hours the solution was cooled to 0°, glacial acetic acid (15 c.c.) was added, and overnight 1 : 5(?) : 7-*trinitro*-m-*nitrobenzenesulphon*-2-*naphthalide* separated in yellow micro-needles, m. p. 248° (decomp.); it recrystallised from glacial acetic acid in pale yellow, matted, silk-like needles, m. p. 262° (decomp.) (Found: N, 14·9; S, 7·27. $C_{16}H_9O_{10}N_5S$ requires N, 15·1; S, 6·9%). When this was hydrolysed, as described above for the dinitro-compound, 1 : 5(?) : 7-*trinitro*-2-*naphthylamine* was obtained, which crystallised from glacial acetic acid (charcoal) in golden yellow needles, m. p. 291—292° (Found: N, 19·9. $C_{10}H_6O_6N_4$ requires N, 20·1%), which would not form a picrate. Attempts to deaminate this compound were unsuccessful.

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TECHNICAL COLLEGES OF BRADFORD AND HUDDERSFIELD. [*Received, September 9th*, 1949.]

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164. *Some Derivatives of 5-Nitro-2-naphthylamine with a Note on its Preparation.*

By HERBERT H. HODGSON and RAYMOND E. DEAN.

From a review of existing methods, it would appear that the most serviceable method for the preparation of 5-nitro-2-naphthylamine is the reduction of 1 : 6-dinitronaphthalene by alkaline hydrosulphide. 5-Nitro-m-nitrobenzenesulphon-2-naphthalide is nitrated further only by excess of nitric acid (*d* 1·5) to give 1 : 5-dinitro-m-nitrobenzenesulphon-2-naphthalide, a compound which monobrominates, probably to 3-bromo-1 : 5-dinitro-m-nitrobenzenesulphon-2-naphthalide. The 2-bromo-5-nitronaphthalene now described completes the set of bromonitronaphthalenes.

Of the methods extant for the preparation of 5-nitro-2-naphthylamine, several involve the simultaneous production of the isomeric 8-nitro-2-naphthylamine. For example, the procedures described by Friedländer and Szymanski (*Ber.*, 1892, **25**, 2076), Morgan and Chazan (*J. Soc. Chem. Ind.*, 1922, **41**, 1T, 61T), and Morgan and Jones (*ibid.*, 1923, **42**, 341T) are based on the addition of β-naphthylamine nitrate to concentrated sulphuric acid at $< -5°$, with the subsequent tedious separation of the two bases by fractional crystallisation of their hydrochlorides, sulphates, or oxalates. The solubilities, however, of the free bases or their salts in

various solvents are so similar, that separation is difficult. The proportions in which the isomerides occur are difficult to determine, since the diagram of the mixed m. p.s is indefinite over a wide range, but from the experimental fact that 5-nitro-2-naphthylamine is relatively much easier to obtain in greater yield and higher purity than the 8-nitro-isomeride, it would appear to preponderate in the mixture.

Hodgson and Crook's method (*J.*, **1936**, 1844), which depends on the nitration of phthalo-β-naphthylimide, is superior from the manipulative point of view, since the higher temperature employed enables more rapid nitration, and a method of hydrolysis of the mixed phthalo-5- and -8-nitronaphthylimides by ethanol–hydrochloric acid (cf. Hey and Lawton, *J.*, 1940, 381) is now described, as an alternative to that by aqueous ammonia under pressure.

It is concluded that the most serviceable method for the preparation of pure 5-nitro-2-naphthylamine in good yield involves the deamination of 1 : 6-dinitro-2-naphthylamine (Hodgson and Turner, *J.*, 1943, 318), and the reduction of 6-nitro-group of the 1 : 6-nitronaphthalene by the aqueous sodium sulphide–sodium hydrogen carbonate–methanol procedure of Hodgson and Birtwell (*J.*, 1944, 75) (cf. also, improvements by Hodgson and Ward, *J.*, 1945, 590, 663, 794; 1948, 242).

The 2-bromo-5-nitronaphthalene, prepared from the 5-nitro-2-naphthylamine by the Sandmeyer reaction, together with the 1-bromo-7-nitronaphthalene (Hodgson and Dean, *J.*, 1950, 818) complete the set of bromonitronaphthalenes.

The further nitration of 5-nitro-*m*-nitrobenzenesulphon-2-naphthalide gives 1 : 5-dinitro-*m*-nitrobenzenesulphon-2-naphthalide, independently of whether the calculated amount or an excess of nitric acid (*d* 1·5) is used, whereas (cf. p. 820) the action of excess of nitric acid (*d* 1·5) on 7-nitro-*m*-nitrobenzenesulphon-2-naphthalide is to give 1 : 5(?) : 7-trinitro-*m*-nitrobenzenesulphon-2-naphthalide. The 1 : 5-dinitro-compound gives a monobromo-derivative to which the structure 3-bromo-1 : 5-dinitro-*m*-nitrobenzenesulphon-2-naphthalide is assigned by analogy with the results of Consden and Kenyon (*J.*, 1935, 1595).

Experimental.

Acid Hydrolysis of the Mixture of Phthalo-5- and -8-nitro-2-naphthylimides.—The mixture (95 g.) was heated under reflux with ethanol (750 c.c.) and hydrochloric acid (225 c.c.; *d* 1·2) for 8 hours, a further quantity of hydrochloric acid (20 c.c.) being added at hourly intervals. At the end of this period, a considerable amount of an orange solid was undissolved; it was filtered off and again heated under reflux as before for 8 hours, but even then an appreciable amount still remained undissolved. The two filtrates were combined, cooled, and stirred into iced water, and the mixture of bases precipitated by ammonia (32 g.; m. p. 70—80°) and dried. Ethanol–sulphuric acid attacked the mixed phthalimides more rapidly, but side reactions led to a decreased yield of the mixed bases.

5-Nitro-m-*nitrobenzenesulphon-2-naphthalide.*—5-Nitro-2-naphthylamine (10 g.) and *m*-nitrobenzenesulphonyl chloride (15 g.) were intimately ground together in a mortar, the mixture heated under reflux for 3 hours with pyridine (30 c.c.), and the solution cooled to 0° and stirred into iced 15% hydrochloric acid (200 c.c.). The resulting *naphthalide* was dissolved in boiling 70% acetic acid (charcoal), and the filtered solution allowed to crystallise (16·2 g.; 81·6%); it recrystallised from hot glacial acetic acid in brown micro-crystals, m. p. 171° (Found: N, 11·4. $C_{16}H_{11}O_5N_3S$ requires N, 11·2%).

Mononitration of 5-Nitro-m-*nitrobenzenesulphon-2-naphthalide.*—The powdered compound (5 g.) was boiled with glacial acetic acid (25 c.c.), the temperature allowed to fall to 50°, and a crystal of sodium nitrite added followed by the dropwise addition with stirring of 2 c.c. of a solution of nitric acid (5·6 c.c.; *d* 1·5) in glacial acetic acid (14·4 c.c.); the temperature rose to 60°, after which it was raised to 75° for 5 minutes, and the mixture kept for 5 hours at room temperature. Glacial acetic acid (20 c.c.) was then added, and the precipitate (5 g.) filtered off, washed with glacial acetic acid and ether, and dried at 100°. The 1 : 5-*dinitro*-m-*nitrobenzenesulphon-2-naphthalide* crystallised from glacial acetic acid in pale yellow needles, m. p. 216° (Found: N, 13·6. $C_{16}H_{10}O_7N_4S$ requires N, 13·4%). Excess of nitric acid (*d* 1·5) afforded the same product. This compound (1 g.) was hydrolysed by sulphuric acid (*d* 1·84) at 50° for 15 minutes and gave 1 : 5-dinitro-2-naphthylamine, which crystallised from glacial acetic acid in golden brown needles, m. p. 193° (Bell, *J.*, 1929, 2784, gives m. p. 191°), and, when diazotised by Hodgson and Walker's method (*J.*, 1933, 1620) and subsequently treated by the cuprous oxide–methanol procedure (cf. Hodgson and Turner, *J.*, 1942, 748; 1943, 86), it gave 1 : 5-dinitronaphthalene which crystallised from ethylene dichloride in yellow plates, m. p. and mixed m. p. with an authentic specimen, 216°.

Reaction of 1 : 5-*Dinitro*-m-*nitrobenzenesulphon-2-naphthalide with Bromine.*—A solution of the naphthalide (5 g.) in pyridine (15 c.c.) was stirred and bromine (0·6 c.c.) added dropwise below 20°, the mixture kept overnight, then cooled to 5° and stirred into iced 15% hydrochloric acid (100 c.c.). The reddish-brown precipitate (5 g.) of 3-*bromo*-1 : 5-*dinitro*-m-*nitrobenzenesulphon-2-naphthalide* was washed with water and dried at 100°; it crystallised from glacial acetic acid in golden-yellow micro-needles, m. p. 234° (Found: N, 11·5; Br, 16·0. $C_{16}H_9O_7N_4BrS$ requires N, 11·3; Br, 16·1%).

2-*Bromo*-5-*nitronaphthalene.*—A solution of 5-nitro-2-naphthylamine (2 g.) in sulphuric acid (5 c.c.; *d* 1·84) at 10° was stirred with one of sodium nitrite (1 g.) in sulphuric acid (5 c.c.; *d* 1·84) at <20°, and, when diazotisation was complete, the mixture was stirred into a solution of cuprous bromide (2·5 g.) in hydrobromic acid (25 c.c.; *d* 1·7). After reaction had ceased the mixture was poured into iced water, the precipitate of 2-*bromo*-5-*nitronaphthalene* filtered off, washed with water, 2% aqueous sodium

carbonate, and water, and dried at 40°. It crystallised from ethanol (charcoal) in light brown rods, m. p. 98—99° (Found: N, 5·6; Br, 31·6. $C_{10}H_4O_2NBr$ requires N, 5·5; Br, 31·7%).

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165. *The Bromination of 6-Nitro-1-naphthylamine.*

By HERBERT H. HODGSON and RAYMOND E. DEAN.

6-Nitro-1-naphthylamine dibrominates in chloroform solution at −5° to give 2 : 4-dibromo-6-nitro-1-naphthylamine whatever the amount of bromine used. The monobromination previously reported by Hodgson and Turner (*J.*, 1943, 392) using the calculated amount of bromine is found to give a mixture of 2 : 4-dibromo-6-nitro-1-naphthylamine and unchanged 6-nitro-1-naphthylamine.

1-BROMO-7-NITRONAPHTHALENE has been prepared recently by the deamination of 1-bromo-7-nitro-2-naphthylamine (see p. 818), and is not identical with the specimen reported by Hodgson and Turner (*J.*, 1943, 392), which was obtained by the deamination of 4-bromo-6-nitro-1-naphthylamine, itself prepared by the apparent monobromination of 6-nitro-1-naphthylamine in chloroform with the calculated amount of bromine. Since it appeared unlikely that monobromination of 7-nitro-2-naphthylamine would occur in any than the 1-position, and therefore that the compound reported by Hodgson and Dean (*loc. cit.*) was 1-bromo-7-nitronaphthalene, the original bromination of 6-nitro-1-naphthylamine has been repeated. Under the conditions previously employed by Hodgson and Turner (*loc. cit.*), it was found that dibromination always occurred with formation of 2 : 4-dibromo-6-nitro-1-naphthylamine, even when only sufficient bromine was used to effect monobromination. This result is in line with the nitration of toluene-*p*-sulphon-1-naphthalide which always gives the dinitro-compound (Hodgson and Walker, *J.*, 1934, 180).

Repeated fractional crystallisation, with microscopic examination, of Hodgson and Turner's original specimen revealed it to be a mixture of unchanged 6-nitro-1-naphthylamine and its 2 : 4-dibromo-derivative, which would account for the analytical data obtained.

EXPERIMENTAL.

Preparation of 2 : 4-*Dibromo-6-nitro-1-naphthylamine.*—A solution of 6-nitro-1-naphthylamine (2·15 g., in chloroform (55 c.c.) was cooled to −5°, and bromine (1·3 c.c.) in chloroform (12 c.c.) was stirred in dropwise during ten minutes. The mixture was kept for 30 minutes at −5° with occasional stirring to ensure completion of the reaction, and the cream precipitate of 2 : 4-*dibromo-6-nitro-1-naphthylamine hydrobromide* (Found: Br, 56·0. $C_{10}H_7O_2N_2Br_3$ requires Br, 56·2%) filtered off and washed with chloroform and ether; it tended to hydrolyse in the air. The salt was basified with ammonia, the 2 : 4-dibromo-6-nitro-1-naphthylamine (2·3 g.) filtered off, washed with water, dried at 100°, and recrystallised twice from ethanol; it was obtained in red needles, m. p. 202° (Found: N, 8·5; Br, 46·0. Calc. for $C_{10}H_6O_2N_2Br_2$: N, 8·1; Br, 46·2%). In an attempt to obtain a monobromo-derivative, the above procedure was repeated with less bromine (0·25 c.c.), whereby a mixture of 2 : 4-dibromo-6-nitro-1-naphthylamine and 6-nitro-1-naphthylamine was obtained.

1 : 3-*Dibromo-7-nitronaphthalene.*—2 : 4-Dibromo-6-nitro-1-naphthylamine (2·1 g.) was dissolved in boiling glacial acetic acid (35 c.c.) and the solution rapidly chilled to 15° to obtain a fine suspension of the amine, which was then diazotised by addition to a stirred solution of sodium nitrite (1 g.) in sulphuric acid (20 c.c.; *d* 1·84) below 20°. After 30 minutes the solution of the diazonium sulphate was stirred into a hot suspension of cuprous oxide (4 g.) in methanol (70 c.c.), and the mixture was stirred for 1 hour and added to iced water (60 c.c.). Next morning the solid was filtered off, washed in the sequence water (300 c.c.), 2% aqueous sodium carbonate (300 c.c.), and water (300 c.c.), and then extracted with boiling ethanol. The extract was filtered, boiled with animal charcoal, and filtered again; the filtrate was allowed to evaporate. The 1 : 3-*dibromo-7-nitronaphthalene* (0·45 g.) crystallised from ethanol in pale yellow rods, m. p. 195° (Found: N, 4·59; Br, 48·0. $C_{10}H_5O_2NBr_2$ requires N, 4·23; Br, 48·3%), which were very sparingly soluble in cold and rather more soluble in hot ethanol.

1 : 2 : 4-*Tribromo-6-nitronaphthalene.*—A solution of the above amine (1·0 g.) in boiling hydrobromic acid (1·3 c.c.; *d* 1·7) and water (7·5 c.c.) was chilled to 0° to give a fine suspension of the hydrobromide) which was then diazotised at 0° with a solution of sodium nitrite (1 g.) in the minimum amount of water. After 30 minutes the filtered solution was stirred into one of cuprous bromide (2·0 g.) in hydrobromic acid (5 c.c.; *d* 1·7) at 60°, and, when the reaction had ceased, the mixture was poured into iced water and the yellow precipitate filtered off, washed in the sequence water (300 c.c.), 2% aqueous sodium carbonate (100 c.c.), and water (300 c.c.), dried at 70°, and dissolved in boiling ethanol (charcoal). This solution

was filtered and allowed to evaporate, whereupon the *tribromo*-compound separated in clusters of bright yellow needles (0·6 g.), m. p. 165° (Found: Br, 58·2. $C_{10}H_4O_4NBr_3$ requires Br, 58·5%).

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166. *The Isomerization of Berberine and Cotarnine Bases in Presence of Alkali.*

By BASIL SKINNER.

The action of potassium hydroxide on aqueous and alcoholic solutions of berberine and cotarnine hydrochlorides has been further investigated by the methods of absorption spectra and electrometric titration. The earlier work of Dobbie, suggesting that quaternary cotarninium hydroxide was converted into the ϕ-base (cf. Hantzsch) in presence of excess of alkali hydroxide, is confirmed; the reaction is shown to be fast, and reversible by mineral acid; the concentration of alkali needed to effect the change is lower in alcoholic than in aqueous solution. Berberinium hydroxide behaves similarly, but is more stable in both solvents. Berberine base has been prepared in a strongly basic solid form, stable for some days. The various types of system covered by Hantzsch and Kalb's term ϕ-base are discussed.

IN spite of the classical investigations by Hantzsch and by Dobbie, some uncertainty seems to exist about the relation of the ammonium and carbinol forms of berberine and cotarnine (cf. Henry, "Plant Alkaloids," 4th Edn., 1949, pp. 203, 333). Extending their observations with the aid of modern techniques, we have, in the main, confirmed their conclusions, although certain modifications have been found necessary.

The term ϕ-ammonium base was coined by Hantzsch and Kalb (*Ber.*, 1899, **32**, 3109) to describe a quaternary base which became transformed, in certain conditions, into a feebly basic isomer, the ϕ-base. The alkaloid cotarnine was cited as an example. Some of its properties pointed to formula (I), whilst others were best explained on the basis of (II) [cf., *e.g.*,

(I.) (II.)

Decker, *J. pr. Chem.*, 1893, [ii], **47**, 222; Day and Kantam, *J. Indian Chem. Soc.*, 1934, **11**, 835). Hantzsch and Kalb concluded that these two, and possibly other forms, existed in equilibrium, and that the free base isomerised instantly on treatment of the hydrochloride with silver oxide in aqueous suspension, since no drift in conductivity occurred on storage. In fact, however, the quaternary base was perfectly stable under these conditions, as is shown below.

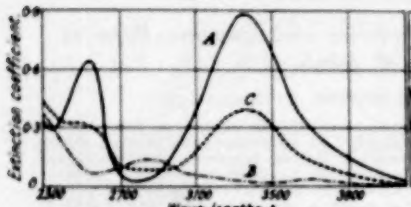
Dobbie, Lauder, and Tinkler (*J.*, 1903, **83**, 598) investigated the problem further by means of absorption spectra. Cotarnine and its derivatives showed two types of spectrum: the first, with two well-marked absorption bands centred on 3278 and 2500 A., was shown by cotarnine and its hydrochloride in aqueous or alcoholic solutions. The second, showing less general absorption, with an ill-defined peak at 2857 A., was shown by solutions of cotarnine in non-hydroxylic solvents, by solutions of ϕ-cotarnine cyanide in all solvents, and by aqueous solutions of cotarnine hydrochloride in presence of a large excess of 2N-sodium hydroxide; at lower concentrations of alkali, spectra intermediate between the two types were obtained. These authors associated the first type of spectrum with the ammonium form (I) and the second with the carbinol form (II): cotarnine and its salts formed the quaternary ion in hydroxylic solvents, except at high concentrations of alkali which favoured the carbinol form. In support of this, Freund, Hantzsch, and Kalb (*Ber.*, 1900, **33**, 380, 2201) showed that ϕ-cotarnine cyanide had the structure (II; CN replaces OH).

As a preliminary step to a more quantitative investigation, we have determined more accurate absorption spectra and made further electrochemical measurements. The treatment was extended to berberine.

The absorption of alcoholic solutions of cotarnine hydrochloride is shown in Fig. 1, curve *A*. The positions of the absorption bands correspond fairly well with those of Dobbie *et al.* In

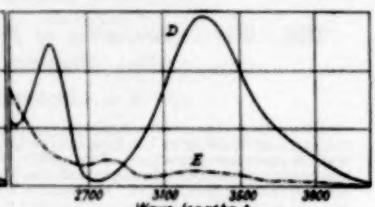
aqueous solution (Fig. 2, curve *D*) the result is very similar. In alcoholic solution in presence of potassium hydroxide, the absorption is as in Fig. 1, curve *B*, at all alkali concentrations down to about 0·001N. At lower concentrations curves intermediate between *A* and *B* are obtained; *e.g.*, curve *C* of Fig. 1 was obtained in presence of $1{\cdot}6 \times 10^{-4}$N-alkali and approximates to that expected from a mixture of 57% of form *A* and 43% of *B*. Although strict precautions to exclude carbon dioxide were taken up to the moment of filling the spectrophotometer cells, it

FIG. 1.



Absorption spectra of: A, *cotarnine hydrochloride in ethanol;* B, *the same* + $7{\cdot}8 \times 10^{-4}$N-KOH; C, *the same* + 0·25N-KOH.

FIG. 2.

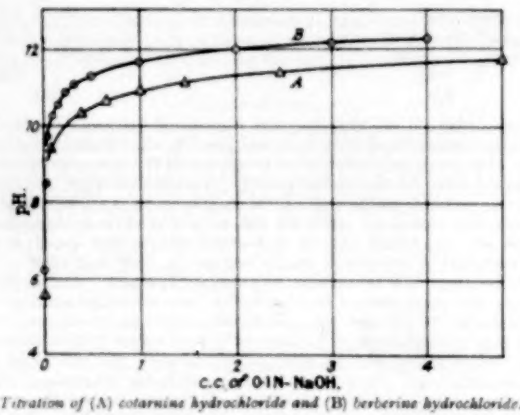


Absorption spectra of: D, *cotarnine hydrochloride in water;* E, *the same* + 0·25N-NaOH.

was not possible to exclude it during the measurements, so that the alkali concentrations must be regarded as maxima rather than as precise.

In aqueous solution, the effect of adding alkali is similar (Fig. 2, curve *E*); but a greater proportion of form *A* exists at equilibrium for a given concentration of alkali than in alcoholic solution, for curve *E*, obtained in presence of 0·25N-sodium hydroxide, appears to be made up of 90% of *B* and 10% of *A*. The initial concentration of cotarnine hydrochloride in all these experiments was 0·016 g. per l. ($5{\cdot}48 \times 10^{-4}$M.). The transition from the yellow (*A*) to the

FIG. 3.



Titration of (A) *cotarnine hydrochloride and* (B) *berberine hydrochloride.*

colourless form appeared to be almost instantaneous, and was immediately reversed by the addition of a slight excess of dilute hydrochloric acid.

A few electrometric experiments were carried out. First a 0·0104N-solution of cotarnine hydrochloride in water was titrated with 0·106N-sodium hydroxide. The changes in pH during titration are shown in Fig. 3: cotarnine behaves as a typical strong base, no buffering action being evident.

The specific conductivity of the same cotarnine hydrochloride solution at 25° was 0·00263,

On addition of 2·5 c.c. of the sodium hydroxide solution to 25 c.c. of the hydrochloride solution so as approximately to neutralise the latter, the conductivity rose to 0·00094, as would be expected of a strong base. After four days the conductivity was 0·00085, indicating the high stability of the quaternary base; this was confirmed by half-neutralising the cotarnine hydrochloride solution with sodium hydroxide and measuring the pH value, which was found to be 11·40; after storage for twelve days in presence of soda-lime, the pH had fallen only to 11·20.

Attempts to prepare the ammonium form of cotarnine in the solid state were unsuccessful owing to decomposition.

The earlier conclusions of Dobbie, Lauder, and Tinkler are thus well borne out. A solution of cotarnine base, in absence of excess of alkali, is stable for days in aqueous solution as the quaternary ion (Form *A*). Addition of alkali causes conversion into the colourless feebly basic isomer to which the carbinol structure is usually assigned, the change being reversed on the addition of acid. This change is brought about very much more easily in alcoholic than in aqueous solution, since the more polar solvent water naturally favours the stability of the quaternary ionic form with its high solvation energy.

The alkaloid berberine present similar difficulties. Gadamer (*Arch. Pharm.*, 1901, **239**, 648) found that addition of aqueous barium hydroxide to berberine sulphate solution and filtration gave a reddish-brown, strongly alkaline solution which he supposed to contain the

(III.) (IV.)

quaternary base, berberinium hydroxide (III). This strongly basic form existed, according to Gadamer, only in solution.

When the solution was treated with an excess of sodium hydroxide, a new ether-soluble form was obtained which gave an oxime; Gadamer called it berberinal, and gave it an aldehyde formula. Tinkler (*J.*, 1911, **99**, 1340) found that the absorption spectrum of berberine hydrochloride in alcoholic solution underwent, on addition of a small quantity of potassium hydroxide, a change similar to that occurring with cotarnine salts. The normal form possessed absorption peaks at 2275 and 2875 A., but in presence of alkali there was one broad absorption band, centred on 2700 A. The latter type of absorption resembled that of α-methyldihydroberberine, which according to Freund and Beck (*Ber.*, 1904, **37**, 4677) had a carbinol structure. Tinkler attributed the new spectrum to the conversion of the berberinium ion (I) into the carbinol (II) which he called berberinol and which was identical with the ether-soluble form.

In the present work the absorption spectrum of alcoholic or aqueous berberine hydrochloride ($3·9 \times 10^{-4}$M.) was found to be as in Fig. 4, curve *A*. In aqueous solution, the addition of sodium hydroxide to a final concentration of 0·25N. had no effect. Very high concentrations of alkali gave a pale pink precipitate, rapidly becoming orange, which may be explained on the basis of Gadamer's observation (*loc. cit.*) that the ether-soluble form of berberine undergoes disproportionation to dihydroberberine and oxyberberine. Slow addition of 2N-sodium hydroxide to a 2×10^{-4}M-solution of the hydrochloride gave a water-soluble yellow precipitate, having the same absorption as the hydrochloride and composed mainly of berberine hydrochloride, salted out of solution.

In alcoholic solution, very low concentrations of alkali change the form of the absorption curve *B* of Fig. 4, being obtained in all cases when the alkali is 2×10^{-2}N. or stronger. Curve *C* ($7·8 \times 10^{-4}$N-KOH) corresponds approximately to that of a mixture of 25% of form *A* and 75% of *B*. The change was again instantaneous and reversed by the addition of acid.

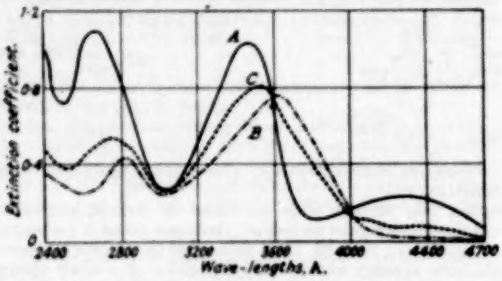
These curves differ considerably from those obtained by Tinkler, who found that alcoholic berberinium chloride solutions show continuously increasing absorption from 3400 to 4500 A. (contrast curve *A* of Fig. 4) and that, even after the addition of potassium hydroxide, absorption was high between 3850 and 4500 A. Further, the wave-lengths of the maxima recorded by Tinkler are not in accord with the present work. More recently determined spectra of berberinium iodide (Feist, Awe, and Etzrodt, *Arch. Pharm.*, 1934, **272**, 820), and of an aqueous solution of berberine base (Chatterjee, *J. Indian Chem. Soc.*, 1942, **19**, 234) resemble Fig. 4, curve *A*, very closely, but no curves intermediate between the two extremes have previously been published. If berberine hydrochloride solution is shaken with silver oxide and filtered, the strongly alkaline

solution gives the same spectrum as a solution of the hydrochloride (curve *A*) which must therefore be attributed to the quaternary berberinium ion (in accord with Tinkler's suggestion). Curve *B* likewise represents the spectrum of berberinol, while curve *C* is that of a mixture of the two substances.

The electrochemical measurements again bear out these conclusions. A 0·004N-solution of berberine hydrochloride, titrated against 0·110N-sodium hydroxide, yielded the curve shown in Fig. 3, which is again that of a typical strong base. The specific conductivity of the same berberine hydrochloride solution at 25° was 0·00111, rising to 0·00345 when 25 c.c. of the solution were nearly neutralised with 4·0 c.c. of the sodium hydroxide solution. This value was unchanged after four days. When the berberinium chloride solution was approximately half-neutralised, the pH was 11·70 and after four days (in presence of soda-lime) was still 11·60, again demonstrating the stability of the strong base. It was in this case possible to isolate the strong base in the solid state by the procedure which failed in the case of cotarnine (cf. p. 827).

Berberine and cotarnine both show, therefore, the same type of isomerism. They differ in the relative stabilities of the ammonium forms to alkali, berberine being more stable in both aqueous and alcoholic solution. It is hoped later to investigate more fully the nature

FIG. 4.



Absorption spectra of: A, *berberine hydrochloride in alcohol;* B, *the same* + 7·8 × 10^{-4}N-KOH; C, *the same* + 0·25N-KOH.

of the common forms of solid cotarnine and berberine bases, and to study quantitatively the equilibrium:

$$R{\cdot}CH{=}\overset{+}{N}{=}R' + \overline{OH} \rightleftharpoons R{\cdot}CH(OH){-}N{=}R' \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

for each alkaloid. From the figures quoted above, approximate values of the equilibrium constant of this reaction can be calculated to be: cotarnine (aqueous solution) 36, (alcoholic solution) 4·7 × 10^9; and berberine (alcoholic solution) 3·8 × 10^9. In view of the possible effect of carbon dioxide on the equilibria, and of the tentative nature of the above equation, confirmation of these values is necessary, although preliminary experiments indicate that the berberine equilibrium in alcoholic solution conforms to the mass law.

The term ψ-base, as used by Hantzsch and Kalb, covers two apparently different types of isomerism: first, where the quaternary base is stable in aqueous solution, but is changed rapidly into the feebly basic isomer on addition of alkali, and, secondly, where the quaternary base decomposes spontaneously on storage, in absence of excess of alkali. Cotarnine, which these authors believed to belong to the second class, is actually an example of the first. The difference is probably more apparent than real; for when the equilibrium constant of the reaction (*A*) is large, adding alkali to a solution of the hydrochloride of the base may give a hydroxyl-ion concentration sufficiently great to promote the isomerisation before neutralisation is complete. If the constant is small, an excess of alkali will be needed to bring about the change, so that the free base will be stable indefinitely in aqueous solution.

EXPERIMENTAL.

Physical Measurements.—Absorption spectra were measured at intervals of 50 A. by means of the Beckman spectrophotometer at room temperature (*ca.* 15°). The slit width was 1 mm. for the range of wave-lengths over which the hydrogen arc was employed (2200—3650 A.) and 0·1 mm. for wave-lengths above 3650 A. It was sometimes necessary to open the slit beyond 1 mm. for the shortest wave-

lengths (2200—2400 A.) in order to obtain a balance with the instrument. The cells were of silica, 1 cm. thick, fitted with loose glass covers.

Measurements of pH were made with a Cambridge pH-meter (bench model) and a glass electrode, at 18°. The response of the glass electrode, which was calibrated against potassium hydrogen phthalate buffers, was slightly irregular at pH values above 10·5, giving high results.

Conductivity measurements were carried out by means of a Wheatstone network circuit with a 1000-cycle Mullard oscillator as current source. The cells were of glass, had a capacity of 25 c.c., closely fitting stoppers, and bright platinum electrodes, and were maintained at 25° by a thermostat. The conductivity water had a conductivity of less than 2×10^{-6}.

Materials.—The berberine hydrochloride was recrystallised twice from water containing a small quantity of hydrochloric acid, and washed twice with cold water before being dried. The cotarnine hydrochloride, obtained from a small pure sample was not recrystallised, but the absorption spectrum confirmed the purity. The aqueous sodium hydroxide used in the titrations was prepared immediately before use by diluting a saturated solution, in order to eliminate carbonate. Absolute alcohol was used throughout, and was redistilled, the first fraction being rejected, for the experiments involving low concentrations of potassium hydroxide, in order to eliminate carbon dioxide.

Berberinium Hydroxide.—0·004M-Berberine hydrochloride (25 c.c.) was shaken with moist silver oxide and filtered. The resulting solution was kept in a desiccator containing calcium chloride and sodium hydroxide for 24 days. The dark brown, hygroscopic residue was treated with 25 c.c. of water, in which it readily dissolved, apart from less than 5% of insoluble matter. The pH of the solution was 11·20 and, on dilution, the liquid had the typical absorption of berberine salts (Fig. 4, curve *A*). It is thus clear that, apart from the small proportion which yielded the insoluble matter, the berberinium hydroxide remained stable in the solid state.

Attempts to Prepare Cotarninium Hydroxide.—Shaking 0·0104N-cotarnine hydrochloride solution with silver oxide and filtration gave a solution (pH 11·80) which decomposed during evaporation on a water-bath. The residual solid was only partly soluble in water and had an odour of volatile amines. Addition of water to give the original volume yielded a solution of pH only 9·2. Decomposition, probably caused by oxidation, also occurred on evaporation of the solution for 24 days in a desiccator containing calcium chloride and sodium hydroxide.

The author thanks Professor R. D. Haworth, F.R.S., and Dr. J. C. Speakman for advice.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, September 20th*, 1949.]

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167. *Fucoidin. Part II. The Hydrolysis of a Methylated Fucoidin prepared from* Fucus vesiculosus.

By J. CONCHIE and E. G. V. PERCIVAL.

L-Fucose (*ca.* 1 part), 3-methyl L-fucose (*ca.* 3 parts) and 2 : 3-*dimethyl* L-*fucose* (*ca.* 1 part) have been identified in the carbohydrate portion of the hydrolysate of a methylated fucoidin. A branched structure in which 1 : 2-α-links predominate is suggested for the polysaccharide.

THE fucoidin used in this series of experiments was prepared from dried, ground *Fucus vesiculosus* collected in the summer months of 1945. The product was comparable with the specimens of fucoidin described in Part I (*J.*, 1950, 717) but the intensive purification was not applied. It had $[\alpha]_D^{18}$ −118°, gave 38% of L-fucose on hydrolysis, and contained Ca 5·9, Mg 0·2, Na 0·9, K 0·1—0·2, and SO_4 32·8%, the sulphate of the ash accounting for half the total sulphate. It required 36 hours at 100° to remove 36% of the total sulphate with N-sodium hydroxide.

Methylation with sodium hydroxide and methyl sulphate gave a product having $[\alpha]_D^{18}$ −107° and containing Ca 5·1, Mg 0·2, Na 0·8, K 0·05, SO_4 25·9, and OMe 15·8%, in which the sulphate in the ash comprised 57% of the total. Evidently, therefore, as for the carrageheen polysaccharides (Buchanan, Percival, and Percival, *J.*, 1943, 51; Dewar and Percival, *J.*, 1947, 1622) the metals combined with the sulphate group were not displaced by sodium during the methylation process. That all the available hydroxyl groups were substituted in the above product was shown by the fact that on treatment with acetic anhydride and pyridine an insignificant amount of acetylation occurred. The acetyl content of fucoidin acetate was found to be 18·0%. If the basic formula is assumed to be $(C_6H_9O_5SO_4Ca_{0.5})_n$ the methylated derivative would contain OMe 12·0%, and the acetate OAc 15·0%. The slightly higher values obtained in practice are attributed to the presence of small amounts of more highly substituted "foreign" polysaccharides rather than to the loss of sulphate groups from the substituted fucose units during methylation.

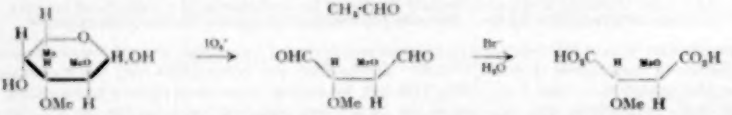
The methylated fucoidin was hydrolysed, and the products were converted into methyl-glycosides and separated by solvent extraction (Brown and Jones, *J.*, 1947, 1344) and on an alumina column. The only compounds to be isolated in quantity were methyl L-fucosides, and the following were found present: methyl-L-fucosides (*ca.* 20%), 3-methyl L-fucosides (*ca.* 57%), and 2 : 3-dimethyl L-fucosides (*ca.* 20%).

The monomethyl sugar was shown to be a derivative of L-fucose by conversion into 2 : 3 : 4-trimethyl α-methyl-L-fucoside. The methyl group was assigned to $C_{(1)}$ for the following reasons. Oxidation gave a lactone, m. p. 136°, $[\alpha]_D$ + 25° ⟶ +75° (in water; 62 hours), with constants comparable with those of 3-methyl D-fuconolactone (digitalonolactone), m. p. 136—140°, $[\alpha]$ −22° ⟶ −70° (60 hours), a specimen of which was prepared from digitalose isolated from *isoemicymarin*. The derived *amide* gave a positive Weerman test.

Further support for the view that we were dealing with 3-methyl L-fucose was derived from a direct comparison on the paper chromatogram with 2-methyl L-fucose, synthesised by the method of McPhillamy and Elderfield (*J. Org. Chem.*, 1939, **4**, 150), and with digitalose (3-methyl D-fucose). There was a distinct separation between 2-methyl L-fucose (R_G 0·56) (Hirst, Hough, and Jones, *J.*, 1949, 928) and digitalose (R_G 0·45), and the material under test was indistinguishable from the latter on the chromatogram. A small quantity of a monomethyl α-methyl-L-fucoside, m. p. 130—132°, $[\alpha]_D$ −173°, which was isolated on one occasion gave on hydrolysis a sugar chromatographically identical with digitalose and must therefore be designated *3-methyl α-methyl-L-fucoside*.

The dimethyl methylglycoside was shown to be a L-fucopyranose derivative by complete methylation to give trimethyl α-methyl-L-fucopyranoside. The methyl groups were assigned to $C_{(3)}$ and $C_{(2)}$ for the following reasons. Oxidation of the dimethyl sugar gave a syrupy lactone, $[\alpha]_D$ +9° ⟶ +47° (22 hours), which was undoubtedly a furanolactone on account of its positive rotation [cf. 2 : 3 : 4-trimethyl L-fuconolactone, $[\alpha]_D$ −138° ⟶ −36° (James and Smith, *J.*, 1945, 746)], thus excluding substitution on $C_{(4)}$. Synthetic 3 : 4-dimethyl L-fucose (Percival and Percival, *J.*, 1950, 690) failed to cause crystallisation on nucleation and 3 : 4-dimethyl α-methyl-L-fucoside had constants markedly different from the crystalline dimethyl methyl-L-fucoside, isolated from the dimethyl fraction in these experiments, which had m. p. 49—51° and $[\alpha]_D$ −190° and is designated *2 : 3-dimethyl α-methyl-L-fucoside*.

Direct chromatographic comparison with 3 : 4-dimethyl L-fucose (R_G 0·67—0·68) showed that although the rate of travel of the dimethyl fucose in question was closely similar (R_G 0·65), by running the paper strips for 48 hours with butanol–ethanol as solvent, the spots developed on spraying with aniline oxalate were distinctly differentiated. Evidence that a methoxyl group was present on $C_{(3)}$ was also given by the fact that the crystalline *dimethyl fuconamide* gave a negative Weerman test, and oxidation of the free sugar with periodate, followed by bromine water, esterification, and amide formation gave D(−)-dimethoxysuccinamide. This product could only arise if methoxyl groups were present on $C_{(2)}$ and $C_{(3)}$: as in

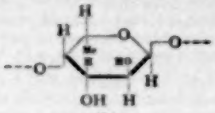


It was only the low yield of amide, attributed to the difficulties which occasionally arise on the oxidation of certain methylated sugars with periodate, which prevented this experiment from being quite conclusive; if the other evidence outlined above is also considered, there seems no reasonable doubt that the dimethyl sugar was, in fact, 2 : 3-dimethyl fucose.

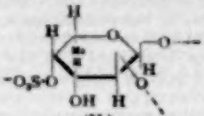
In connection with the above work on partly methylated fucoses, attention should be drawn to the virtual failure of the periodate oxidation method as a test for the presence of a free hydroxyl group on $C_{(4)}$ in partly methylated 6-deoxyhexoses. The method for estimating fucose by periodate oxidation and conversion into acetaldehyde (Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1941, **63**, 1456; Cameron, Ross, and Percival, *J. Soc. Chem. Ind.*, 1948, **67**, 161) was applied to the monomethyl fucose (3-methyl fucose) and the dimethyl fucose (2 : 3-dimethyl fucose). Only one-third of the theoretical yield of acetaldehyde was obtained in each case, although this is much greater than the yield (5%) from 2 : 3-dimethyl rhamnose (Percival and Percival, *loc. cit.*). These results recall similar difficulties with partly methylated hexoses, for Jeanloz (*Helv. Chim. Acta*, 1944, **27**, 1509) and Bell, Palmer, and Johns (*J.*, 1948, 992) showed that in the oxidation of methylated sugars such as 2 : 3 : 4-trimethyl glucose, 2 : 4-dimethyl galactose, and 3-methyl glucose by periodate in buffered solutions, the yield of formaldehyde was much lower than the theoretical.

Before an attempt is made to draw a preliminary picture of the possible structure of fucoidin, one important fact should be noted. Since the sulphate groups are stable to alkali (apart from the fairly rapid initial removal of *ca.* 10% of the total sulphate which will require further

study), it is clear that the main linkage of L-fucopyranose units cannot be through the hydroxyl group on $C_{(4)}$ as the hydroxyl groups on $C_{(3)}$ and $C_{(4)}$ are *trans* to one another (I). A sulphate



(I)

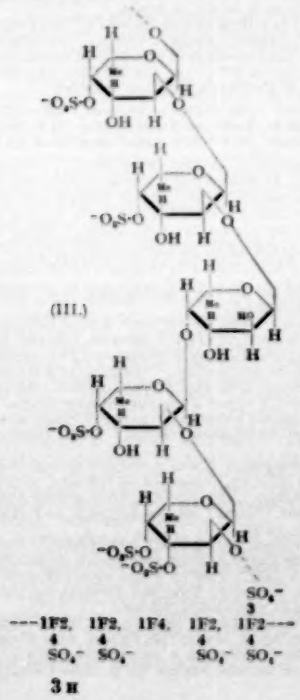


(II)

group in either of these positions would be readily eliminated by alkali (Percival, *Quart. Rev.*, 1949, **3**, 369). The isolation of 3-methyl L-fucose leaves only one possible arrangement (II) for those residues carrying one free hydroxyl group, namely a 1 : 2-linkage with the sulphate on $C_{(4)}$. Because of the strongly negative rotations of fucoidin and its derivatives, these junctions are considered to be predominantly of the α-type.

There are two possible ways of accounting for the free fucose residues in methylated fucoidin, excluding the possibility of incomplete methylation owing to steric effects. First, some fucose residues might carry two sulphate groups, a possibility by no means out of the question since the proportion of sulphate to fucose in the original fucoidin is somewhat higher than is demanded by a 1 : 1 ratio, although contamination with a galactan sulphate would also explain this. The 2 : 3-dimethyl fucose could be explained by the appearance of occasional 1 : 4-linkages, and these residues would require to be unsubstituted by sulphate groups (cf. III).

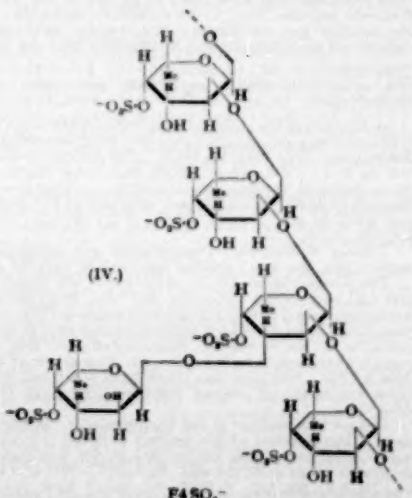
If the conclusions as to the main structural feature are correct, the 2 : 3-dimethyl fucose could not arise as a result of the loss of sulphate groups during methylation since this would produce the 3 : 4-isomer.



(III.)

---1F2, 1F2, 1F4, 1F2, 1F2---
4 4 4 4
SO_4^- SO_4^- SO_4^- SO_4^-

3 H



(IV.)

F4SO_4^-
1
3
---1F2, 1F2, 1F2, 1F2---
4 4 4 4
SO_4^- SO_4^- SO_4^- SO_4^-

F = L-Fucopyranose.

Another possible explanation is that the free fucose originates from branching points carrying terminal groups having free hydroxyls on $C_{(3)}$ and $C_{(4)}$. From the proportions of the various sugars isolated there would be an average of one such branch in every five fucose units (cf. IV).

For either of the two possibilities it will be observed that one equivalent of periodate would be consumed for each unit of five fucose residues. Because of the presence of impurities, this figure cannot be determined with any accuracy at present, but, if the galactose, xylose, and uronic acid known to be present are assumed to be linked by 1 : 4-linkages and a correction is made for the consumption of periodate by these materials, fucoidin reacts with M/10-sodium periodate in 24 hours so that one equivalent of periodate is accounted for by 880 g. of the " ideal " polysaccharide, which corresponds to between three and four monosaccharide units.

Before anything approaching the last word on the constitution of fucoidin can be written, it will be necessary to study more highly purified specimens, and preparations from different algae. Progress will undoubtedly be slow for technical reasons, but this preliminary study may stimulate other workers to attack this problem, which has added interest owing to the discovery by Vasseur (*Acta Chim. Scand.*, 1948, **2**, 900) of fucosan sulphates in the jelly coat of sea-urchin eggs of the species *Strongylocentrus drobachiensis*, *Echinocardium cordatum*, and *Paracentrotus lividus*.

Experimental.

Preparation of the Polysaccharide.—The polysaccharide was extracted as described in Part I (*loc. cit.*). For this investigation specimens of *Fucus vesiculosus* (May–June, July, 1945 samples) kindly supplied by The Scottish Seaweed Research Association, Musselburgh, were used. Purification was effected by allowing a solution of the polysaccharide in water to stand over " Filter-Cel " for several days, followed by filtration, concentration, and pouring into alcohol. The process was repeated till a constant fucose content was obtained. The resulting white fibrous product had $[\alpha]_D^{18}$ −118°. For all quantitative work the polysaccharide was dried over phosphoric oxide at 50°/15 mm. to constant weight [Found : ash (as sulphate), 24·1; Ca, 5·9; Na, 0·9; Mg, 0·2; K, 0·1 – 0·2; SO_4 (total), 32·8%; SO_4 (in ash), 17·6%]. Estimation of fucose by periodic acid oxidation (Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1941, **63**, 1456; Cameron, Ross, and Percival, *J. Soc. Chem. Ind.*, 1948, **67**, 161) gave 37·8% of fucose.

Hydrolysis of Fucoidin with N-Sodium Hydroxide at 100°.—The polysaccharide (1·1082 g.) was heated with N-sodium hydroxide (200 c.c.) at 100° in the presence of barium chloride (1·283 g.). At definite intervals, samples (15 c.c.) were withdrawn, water (15 c.c.) and dilute acetic acid (5 c.c.) were added, and the solution was centrifuged. The residual combined sulphate in 50 c.c. of the solution was then determined by hydrolysis with hydrochloric acid and weighing of the barium sulphate produced :

Time (hrs.)	0	½	1	4	10	20	30	36	48	56	72
Residual sulphate ($BaSO_4$, mg.)	48·5	45·6	43·0	41·2	38·9	38·2	32·0	30·9	25·1	24·1	20·0
Hydrolysis, %	0	6·0	11·4	15·0	19·8	26·1	34·1	36·4	48·2	50·3	58·7

Acetylation of Fucoidin.—The polysaccharide (2 g.) was dissolved in distilled water (30 c.c.), pyridine (120 c.c.) was added, and the pyridine–water azeotrope distilled off at 50°/15 mm (Pacsu and Mullen, *J. Amer. Chem. Soc.*, 1941, **63**, 1487). The distillation was continued till the volume of residual solution was *ca.* 30 c.c., a brown gelatinous mass being obtained. Pyridine was added to bring the volume to 50 c.c., followed by acetic anhydride (25 c.c.) added slowly, with shaking and cooling. After being left in the dark (2 days) the acetate was separated at the centrifuge, washed with pyridine, alcohol, and ether, and dried, to give a white powder (2 g.) [Found : $CH_3{\cdot}CO$, 18·0. Calc. for $C_6H_4O_3(CO{\cdot}CH_3)_5Ca_{0.5}$: $CH_3{\cdot}CO$, 15·0%].

Typical Methylation.—Deacetylation and methylation proving no more satisfactory than direct methylation, the direct method was used throughout the investigation.

The polysaccharide (10 g.), dissolved in the minimum of water, was treated with methyl sulphate (240 c.c.) and sodium hydroxide (672 c.c.; 30%) in one-eighth portions every 2 minutes, followed by methyl sulphate (120 c.c.) and sodium hydroxide (208 c.c.; 30%) in one-eighth portions every 10 minutes, the solution being stirred and the temperature kept at 50° during the methylation. The solution was then heated to 85° for 30 minutes, cooled, neutralised with glacial acetic acid, and dialysed against running water till sulphate-free (10 days). On evaporation at 45°/15 mm. a brown glass was obtained (Found : OMe, 7·2%). This glass was taken up in water and the methylation procedure repeated 3 times, after which the methoxyl content remained unchanged on further methylation (Found : OMe, 15·8%); yield, 6·8 g.

To ascertain whether or not the polysaccharide was fully methylated, it was acetylated as described above. Examination of the product obtained (Found : CH_3CO, < 1%) appeared to indicate, within experimental error, that the polysaccharide was fully methylated. The product, after drying over phosphoric oxide at 50°/15 mm., had $[\alpha]_D^{18}$ −107° (*c*, 1·0 in water) [Found : ash (as sulphate) 21·2; Ca, 5·1; Na, 0·8; Mg, 0·2; K, 0·05; SO_4 (total), 25·9; SO_4 (in ash), 14·8%].

Hydrolysis of the Methylated Polysaccharide.—The above product (5·01 g.) was hydrolysed at 100° with oxalic acid (200 c.c.; 3%) to constant rotation. The solution was neutralised with barium carbonate and worked up in the usual way to give a yellow syrup (3·2 g.), $[\alpha]_D^{18}$ −54·0° (*c* 1·0 in water) (Found : OMe, 20·4%). Estimation of fucose by periodic acid oxidation (Cameron, Ross, and Percival, *loc. cit.*) gave 30·4% as the apparent fucose content or 33·0% calculated as monomethyl fucose.

Glycopyranoside Formation.—The hydrolysed methylated polysaccharide (8·9 g.) was boiled with methanolic hydrogen chloride (400 c.c.; 2%) until non-reducing (5 hours), neutralised with silver carbonate, evaporated, and extracted with alcohol, to give on evaporation a yellow syrup (5·8 g.). Fractionation by distillation in a high vacuum was unsuccessful, but one fraction (b. p. 125—150°/0·1

mm.; n_D^{15} 1·4717; OMe, 29·8%) gave, on hydrolysis and osazone formation, a small yield of an osazone, m. p. 178—179° (decomp.) (Found: OMe, 9·2. Calc. for $C_{19}H_{24}O_4N_4$: OMe, 8·7%), which was presumed to be 3-methyl phenylfucosazone.

Fractionation by Chromatographic Adsorption on Alumina.—The glycosides were dissolved in chloroform–light petroleum (1 : 1) and introduced into a column (30 × 2 cm.) of activated alumina (Spence and Sons: Grade H) suspended in the same solvent. The column was developed first with the same mixture, then with increasing proportions of chloroform, followed by mixtures of chloroform and methanol, and finally pure methanol. Six fractions were obtained: (1) 1·036 g., n_D^{15} 1·4590, (2) 0·124 g. (partly crystalline), n_D^{15} 1·4580, (3) 1·080 g. (partly crystalline), n_D^{15} 1·4670, (4) 1·192 g., n_D^{15} 1·4688, (5) 0·878 g., and (6) 0·182 g. Recovery was 88%.

Examination of fraction (1). This fraction (0·97 g.) on distillation gave fractions (1a) 0·476 g., b. p. 75—80°/0·03 mm., n_D^{15} 1·4549 (Found: OMe, 46·6%), and (1b) 0·385 g., b. p. 90—110°/0·03 mm.; n_D^{15} 1·4601 (Found: OMe, 47·7. Calc. for $C_4H_6O_3(OCH_3)_2$: OMe, 45·1%). Later experiments using the paper chromatogram showed the two fractions to be identical.

Formation of 2 : 3 : 4-trimethyl α-methyl-L-fucoside from fraction 1a. This fraction (0·2 g.), after two treatments with Purdie's reagents, gave white needles (0·18 g.), m. p. 84—89°, subliming *in vacuo*, $[\alpha]_D^{15}$ −192° (*c*, 1·08) (Found: OMe, 56·1. Calc. for $C_{10}H_{20}O_5$: OMe, 56·3%). A mixed m. p. determination with authentic 2 : 3 : 4-trimethyl α-methyl-L-fucoside showed no depression.

Periodic acid oxidation of fraction 1b. *Isolation of* D(−)*-dimethoxysuccinamide.* The syrup (0·2 g.) was hydrolysed with sulphuric acid (50 c.c.; 0·1N.) for 8 hours at 100° ($[\alpha]_D$ −61° ⟶ −1°) and the solution worked up in the usual manner. To the syrup so obtained was added periodic acid (20 c.c.: 0·5M.), and the solution was set aside for 20 hours at room temperature. After thorough aeration to remove the acetaldehyde, barium chloride (1·22 g.) was added to the solution, followed by barium carbonate in excess. The residue, after filtration, was extracted with a small quantity of water, and the extract added to the filtrate. Oxidation with bromine (3 c.c.) gave a small quantity of syrup which was boiled with methanolic hydrogen chloride (50 c.c.; 2·5%) for 5 hours and worked up in the usual way. Treatment of the resulting syrup with methanolic ammonia (2 c.c.) for 3 days at 0° gave a crystalline solid mixed with syrup. The long needle-shaped crystals (12 mg.) were washed with alcohol and dried, and then had m. p. 262—263° and $[\alpha]_D^{15}$ −92° (*c*, 2·01 in water) (Found: OMe, 34·8. Calc. for $C_6H_{12}O_4N_2$: OMe, 35·3%). A mixed m. p. determination with authentic D(−)-dimethoxysuccinamide, m. p. 265—268°, $[\alpha]_D$ −94°, showed no depression, but one with (±)-dimethoxysuccinamide showed a large depression.

Examination of crystalline portion of fraction 2. 2 : 3-*Dimethyl α-methyl-L-fucoside.* After fraction 2 had been dried on a tile and recrystallised from light petroleum (b. p. 40—60°) a small quantity of crystals (12 mg.) was obtained, having m. p. 49—51°, $[\alpha]_D^{15}$ −190° (*c*, 1·4 in water) (Found: C, 52·3; H, 8·6; OMe, 44·3. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7; OMe, 45·1%).

Examination of fraction 3. *Isolation of* 3-*methyl α-methyl-L-fucoside.* This fraction was partly crystalline, and an attempt was made to obtain a greater yield of crystals by fractionation using a column of alumina and developing with chloroform–methanol (3 : 1). The crystalline fraction so obtained was dried on a porous tile and recrystallised from ethyl acetate, and then had m. p. 130—132°, $[\alpha]_D^{15}$ −173° (*c*, 0·4 in water) (Found: C, 50·3; H, 8·4; OMe, 32·1. $C_8H_{16}O_5$ requires C, 50·0; H, 8·3; OMe, 32·3%).

Hydrolysis with sulphuric acid (0·1N.) for 8 hours gave the free sugar as a syrup, $[\alpha]_D^{15}$ −94° (*c*, 0·51) Found: OMe, 17·8. $C_7H_{14}O_5$ requires OMe, 17·4%). This sugar was compared on the same paper) chromatogram with synthetic 2-methyl L-fucose (R_6 0·56) and digitalose (3-methyl D-fucose) (R_6 0·45), obtained from *iso*emicymarin (see below). The R_6 value (0·45) obtained for the sugar was identical with that of digitalose.

Examination of fractions 4, 5, *and* 6. Fraction 4, when examined by paper chromatography, proved to be a mixture of di- and mono-methyl methylfucosides with a little free methylfucoside. An attempted separation by means of cold extraction with chloroform did not give very satisfactory results, though from one monomethyl fraction an osazone, m. p. 172—176° (decomp.), which contained a methoxyl group, was obtained, indicating the presence of a free hydroxyl group on $C_{(2)}$.

Fractions 5 and 6 gave, on storage, a quantity of crystals of α-methyl-L-fucoside which were separated, drained on a tile, and recrystallised from ethyl acetate, to give m. p. 154—156°, $[\alpha]_D^{15}$ −197° (*c*, 1·1 in water) (Found: OMe, 17·2. Calc. for $C_7H_{14}O_5$: OMe, 17·4%). The remaining syrup was found, on hydrolysis with sulphuric acid (0·1N.) and examination by paper chromatography, to contain 3-methyl fucose, fucose, and a trace of hexose. Fucose estimations on these hydrolysed syrups gave: fraction (5) 93·1%; fraction (6) 87·8% calculated as fucose.

Fractionation by Solvent Extraction.—Methylated glycosides from the methylated polysaccharide (5 g.) were dissolved in water (25 c.c.) and extracted for 15·5 hours with light petroleum (b. p. 40—60°) to give fraction *A* (0·38 g.), n_D^{15} 1·4499. This fraction was distilled in a high vacuum, giving a clear syrup (0·28 g.), b. p. 83—87°/0·04 mm., n_D^{15} 1·4442 (Found: OMe, 49·8%). Extraction with chloroform for (*a*) 4½ hours gave fraction *B* (1·80 g.), n_D^{15} 1·4610 (Found: OMe, 40·0%), (*b*) 23½ hours gave fraction *C* (1·66 g.), n_D^{15} 1·4735 (Found: OMe, 28·6%), and (*c*) 34 hours gave fraction *D* (0·24 g.), partly crystalline (Found: OMe, 30·9%). Evaporation of the aqueous solution gave fraction *E* (0·97 g.) (Found: OMe, 16·4%). Recovery was 98%.

Examination of fraction A. This fraction on hydrolysis and examination by paper chromatography was found to consist of the dimethyl fucose already examined and traces of 2 : 3 : 4-trimethyl fucose and one or more highly methylated hexoses or pentoses. There was also a possible indication of the presence of a small amount of a methylated uronic acid.

Fractionation and examination of fraction B. This portion was subjected to further fractionation by passage through an alumina column (20 × 2 cm.), using for development first chloroform and then methanol. Two fractions were obtained: (*a*) with chloroform, fraction *B*1 (0·79 g.), b. p. 100—110°/0·04 mm., n_D^{15} 1·4590 (Found: OMe, 46·3%; apparent percentage of fucose (see Introduction), 32·4%), and (*b*) with methanol, fraction *B*2 (0·87 g.), n_D^{15} 1·4669 (Found: OMe, 31·1%; apparent percentage of fucose, 34·2).

Fraction *B*1 was hydrolysed with sulphuric acid (0·1N.), giving a syrup, $[\alpha]_D^{18}$ +4·6° (*c*, 3·0 in water) (Found: OMe, 32·1%), which did not crystallise even on storage for several months. Nucleation with authentic 3 : 4-dimethyl L-fucose did not induce crystallisation. Comparison of the two sugars by paper chromatography showed they had very similar R_G values (*J.*, 1950, 690), but on prolonging the experiment [48 hours in butanol–ethanol–water (40 : 10 : 50)] it was possible to differentiate between the spots after spraying with aniline oxalate.

Formation of lactone from hydrolysed fraction B1. *2 : 3-Dimethyl* L-*fucofuranolactone.* The dimethyl fucose (0·18 g.) in water (5 c.c.) was treated with bromine (1·5 c.c.) at room temperature till non-reducing (30 hours). After aeration, neutralisation with silver carbonate, treatment with hydrogen sulphide, etc., and lactonisation, a clear syrup (0·1 g.) was obtained, having b. p. 130°/0·04 mm. (Found: OMe, 34·8%; 16 mg. required 1·67 c.c. of 0·027N-sodium hydroxide for neutralisation. $C_8H_{14}O_5$ requires OMe, 32·6%; 1·79 c.c.). The lactone showed $[\alpha]_D^{18}$ +9° (5 minutes), +10° (30 minutes), +11° (1 hour), +23° (3 hours), +28° (4 hours), +34° (8 hours), +37° (12 hours), +40° (15 hours), +47° (22 hours, constant) (*c*, 1·6 in water), the positive rotation indicating the presence of a dimethyl γ-L-fuconolactone; cf. 2 : 3 : 4-trimethyl L-fuconolactone $[\alpha]_D$ −138° ⟶ −36° (James and Smith, *loc. cit.*).

2 : 3-Dimethyl L-*fuconamide.* The above lactone (40·4 mg.) was treated with methanolic ammonia (2 c.c.) at 0° for 48 hours. On evaporation of the solvent at 14°/15 mm. the entire solution crystallised, giving a white solid which, recrystallised from light petroleum (b. p. 60—80°), had m. p. 78—79°, $[\alpha]_D^{18}$ +30·2° (*c*, 0·86 in water) (Found: OMe, 30·0. $C_8H_{15}O_4N$ requires OMe, 30·3%). The *amide* gave a negative Weerman test, indicating that the hydroxyl group on $C_{(3)}$ was substituted by methoxyl.

3-Methyl L-*fucofuranolactone and its amide.* The hydrolysed fraction *B*2 was oxidised with bromine till non-reducing. After the usual treatment followed by lactonisation, a white crystalline product, m. p. 132—136°, was obtained. This gave $[\alpha]_D^{18}$ +25° (10 minutes), +37° (30 minutes), +46° (1 hour), +46° (2 hours), +47° (3 hours), +50° (7 hours), +53° (12 hours), +61° (19 hours), +74° (32 hours), +75° (48 hours), +75° (62 hours, constant), (*c*, 0·95 in water). This indicated a γ-lactone, and thus $C_{(4)}$ was occupied by a hydroxyl group in the methylated fucose.

The lactone gave a syrupy *amide*, $[\alpha]_D^{18}$ +17·2° (*c*, 0·6 in water) (Found: OMe, 16·7. $C_7H_{13}O_4N$ requires OMe, 16·1%). The amide (40 mg.) yielded hydrazodicarbonamide (15 mg.), m. p. 253—255° unchanged on admixture with an authentic specimen.

Paper chromatography. Examination of hydrolysed fraction *B*2 and comparison with 2-methyl L-fucose and digitalose showed that, as with fraction 3, the R_G value (0·45) was the same as that of digitalose.

Fractions C *and* D. Both fractions were observed, on hydrolysis and examination by paper chromatography, to be identical with fraction *B*2. Periodic acid oxidation of hydrolysed fraction *E* gave acetaldehyde corresponding to 34·5% of monomethyl fucose.

Derivatives from fraction C. *3-Methyl* L-*fuconamide.* Oxidation with bromine, followed by the usual treatment, gave the lactone as a syrup, b. p. 180°/0·04 mm., n_D^{18} 1·4750 [Found: OMe, 18·1%; 14 mg. required 2·67 c.c. of 0·025N-sodium hydroxide for neutralisation. Calc. for $C_7H_{12}O_4$: OMe, 17·6%; 2·66 c.c.]. This lactone in water showed $[\alpha]_D$ +20° (20 minutes), +20° (30 minutes), +22° (1 hour), +26° (2 hours), +28° (3 hours), +29° (4 hours), +34° (6 hours), +45° (12 hours), +50° (18 hours), +52° (21 hours), +59° (28 hours), +67° (36 hours), +74° (42 hours, constant) (*c*, 0·7 in water). 2 C.c. of the above solution required 2·66 c.c. of 0·02505N-sodium hydroxide (Calc.: 2·66 c.c.).

Treatment of the above lactone with methanolic ammonia gave a crystalline *amide*, m. p. 176—180°, $[\alpha]_D^{18}$ +16·4° (*c*, 0·58 in water) (Found: OMe, 16·4. $C_7H_{13}O_4N$ requires OMe, 16·1%). This amide (43 mg.) gave hydrazodicarbonamide (20 mg.), m. p. 256° (decomp.) unchanged on admixture with an authentic speciman.

Fraction E. *Isolation of α-methyl* L-*fucoside.* This fraction partly crystallised, and after drying on a porous tile and recrystallisation from ethyl acetate had m. p. 154—155° not depressed on admixture with authentic α-methyl-L-fucoside, $[\alpha]_D^{18}$ −194° (*c*, 1·1) (Found: OMe, 17·0. Calc. for $C_7H_{14}O_5$: OMe, 17·4%). Examination by paper chromatography after hydrolysis showed the fraction to consist of fucose with a trace of a hexose. A fucose estimation with periodic acid gave 90·3% fucose.

Extraction of 3-*Methyl* D-*Fucose from* iso*Emicymarin.*—The cardiac glycoside emicymarin is a much better source of digitalose (3-methyl D-fucose), but unfortunately no samples of this compound were available.

*iso*Emicymarin (0·3 g.), obtained through the kindness of Dr. S. Smith, Wellcome Chemical Research Laboratories, Beckenham, was dissolved in 50% alcohol (150 c.c.) containing 5% of hydrochloric acid and hydrolysed for 4 hours on a boiling water-bath. After extraction several times with chloroform, the aqueous fraction was neutralised with silver carbonate. Removal of the silver salts and evaporation gave a small yield of syrup (60 mg.).

Preparation of 3-*Methyl* D-*fuconolactone.*—Part of the syrup (54 mg.) was oxidised with bromine for 3 days. After the usual treatment and lactonisation a small amount of needle-shaped crystals, m. p. 136—140°, was obtained. This gave $[\alpha]_D^{18}$ −22° (5 minutes), −24° (1 hour), −27° (3 hours), −31° (5 hours), −35° (9 hours), −38° (12 hours), −45° (17 hours), −53° (24 hours), −63° (36 hours), −68° (42 hours), −70° (60 hours, constant) (*c*, 0·9 in water).

Oxidation of Fucoidin with Sodium Periodate [*with* A. G. Ross].—Fucoidin (0·520 g.) from *Himanthalea lorea* (see Part I, *loc. cit.*) was dissolved in sodium metaperiodate solution (40 c.c.; 0·1M.) and continuously shaken. Samples (5 c.c.) were removed at intervals and the remaining periodate estimated, after 15 minutes, with iodine (0·1N.) after the addition of sodium hydrogen carbonate (1 g.), sodium arsenite (20 c.c.; 0·1N.), and potassium iodide (1 g.) (Found: uptake of sodium periodate in g.-equivs./100 g. of fucoidin, 4 hours 0·088, 24 hours 0·131).

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KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, December 13th*, 1949.]

168. *Decomposition Reactions of the Aromatic Diazo-compounds. Part XII. The Reaction between Diazo-compounds and Potassium Ferrocyanide.*

By M. C. Ford, William A. Waters, and H. T. Young.

The conditions under which aromatic diazo-compounds react with potassium ferrocyanide solution to yield arylazodiaryls have been studied, and it has been found that the decomposition proceeds most smoothly at pH 4—5 in the presence of a sodium acetate buffer. Yields of about 20% can be obtained with substituted aromatic amines, $R{\cdot}C_6H_4{\cdot}NH_2$, when the substituent R = Me or Cl, but both with the strongly *op*-directive substituent OMe and with the *m*-directive substituent NO_2 the yield falls to under 0·5%.

Both degradative and synthetic reactions have been carried out to establish the structures of the unsymmetrical arylazodiaryls obtained from *o*- and *p*-toluidine, *p*-chloroaniline, and α-naphthylamine. When the substituent R occupies the *p*-position to the nitrogen in the original amine, the reaction product is the 2-aryl derivative of a 4 : 4′-substituted azobenzene, and when R is an *o*-substituent the product is a 4-aryl derivative of a 2 : 2′-substituted azobenzene. Isomeric reaction products do not appear to be formed in appreciable amount.

Possible mechanisms of this reaction are discussed.

In Part XI (*J.*, 1946, 1154) Saunders and Waters drew attention to the fact that 4-phenylazobenzene (I; R = H) can be prepared by treating aqueous solutions of benzenediazonium salts with potassium ferrocyanide, and suggested that free phenyl radicals might play some part in this rather unusual diazo-decomposition. We have now made an experimental study of this reaction, which since its discovery by Griess (*Ber.*, 1876, **9**, 132) has received scarcely any attention during this century, and we have established the structures of the unsymmetrical arylazodiaryls which can be prepared from diazotised *o*- and *p*-toluidine, *p*-chloroaniline, and α-naphthylamine.

The account given by Griess is very brief, and it was left to Locher (*Ber.*, 1888, **21**, 911) to show that Griess's reaction product, $C_{12}H_{14}N_2$, m. p. 150°, was probably 4-phenylazobenzene since it could be reduced to a mixture of aniline and *p*-aminodiphenyl (m. p. 50—51°). We have confirmed this work and have obtained from Griess's azo-compound pure *p*-acetamidodiphenyl having a melting point which was unchanged after admixture with an authentic specimen.

On investigating the conditions under which 4-phenylazobenzene can be obtained from aqueous solutions of benzenediazonium sulphate or chloride and potassium ferrocyanide, we found that, though the evolution of nitrogen commences immediately the reactants are mixed at, or below, room temperature, the yield of the desired reaction product is greatly increased by first buffering the diazonium salt solution to pH 4—5 by addition of an excess of sodium acetate. However, if the diazo-solution is first made neutral with sodium hydroxide or sodium hydrogen carbonate, only tarry products result. The organic reaction product usually separates as a filterable solid as the nitrogen is evolved. The reaction can in every case be completed at room temperature and it leaves a purple or brown aqueous solution which does not couple with alkaline β-naphthol. In some cases there was an indication that an intermediate solid diazonium ferrocyanide may be formed. After the reaction is over, the aqueous solution contains ferricyanide anions, showing that the reaction is essentially a reduction of the aromatic diazo-compound. The yields of the desired organic products were not appreciably altered by changing from the procedure of adding aqueous potassium ferrocyanide to a stirred buffered solution of benzenediazonium sulphate to the reverse procedure of adding the diazo-solution to the stirred ferrocyanide (contrast the Sandmeyer reaction), and so for convenience the second procedure was generally used with the other diazonium compounds.

When working with diazotised aniline and *p*-toluidine, there was no advantage in taking much more potassium ferrocyanide than the amount indicated by the simplified equation

$$2R{\cdot}C_6H_4{\cdot}N_2^+ + 2[Fe(CN)_6]^{4-} \longrightarrow R{\cdot}C_6H_4{\cdot}C_6H_3R{\cdot}N_2{\cdot}C_6H_4R + H^+ + 2[Fe(CN)_6]^{3-}$$

but when working with diazotised *p*-chloroaniline the yield of arylazodiaryl could be almost doubled by using 2 moles of ferrocyanide per mole of diazo-compound. In no case, however, was the overall yield of pure material more than 20%.

The products remaining in the aqueous layer were regularly investigated. These solutions invariably smelt of *iso*cyanide and, when heated, deposited Prussian-blue. On steam-distillation, however, they yielded only very small amounts of the nitriles, $R{\cdot}C_6H_4{\cdot}CN$, corresponding to the original amines, and no detectable amounts of the corresponding phenols,

R·C_6H_4·OH, or of hydrocarbons R·C_6H_5·H or R·C_6H_4·C_6H_4·R. Small amounts of hydroxyazo-dyes were always formed. When diazonium chlorides are used instead of diazonium sulphates no significant quantities of aryl chlorides can be detected. Hence this diazo-reaction does not correspond with the normal decomposition of a diazonium cation in water: $Ar{\cdot}N_2^+ + H_2O \longrightarrow Ar{\cdot}OH + H^+$ (cf. Part X, *J.*, 1942, 266, for Type I reactions of the aromatic diazo-compounds), and is not clearly related to the Sandmeyer reaction which Cowdrey and Davies (*J.*, 1949, S 48) have recently shown to be an intramolecular decomposition of a complex salt. It is therefore probable that the initial reaction which involves the oxidation of the ferrocyanide anion is a one-electron transfer, as indicated in equations (1*a*) and (1*b*), and that the final azo-compounds result from reactions involving free organic radicals. The recent demonstration by Merz and Waters (*J.*, 1949, 2427) that free aryl radicals do not react with water molecules adds support to this view.

$$(1a) \quad Ar{\cdot}N_2^+ + [Fe(CN)_6]^{4-} \longrightarrow Ar{\cdot}N_2{\cdot} + [Fe(CN)_6]^{3-}$$

or

$$(1b) \quad Ar{\cdot}N{:}N{\cdot}OH + [Fe(CN)_6]^{4-} \longrightarrow Ar{\cdot}N_2{\cdot} + (OH)^- + [Fe(CN)_6]^{3-}$$

followed by

$$(2) \quad Ar{\cdot}N{:}N{\cdot} \longrightarrow Ar{\cdot} + N_2$$

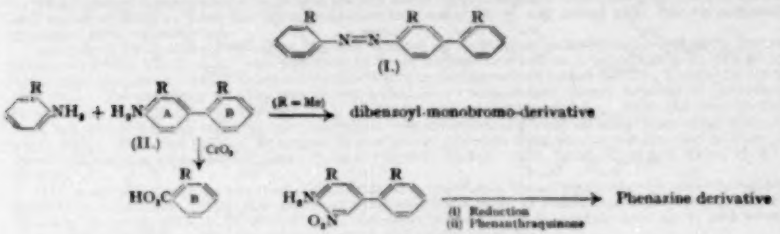
As suggested in Parts X and XI, electron-transfer potentials may be significant in determining yields in reactions such as (1) above, and in this connection it was observed that the yield of isolatable arylazodiaryl became very small indeed when the selected aromatic diazo-compound contained either a strongly electron-donating ($+T$) substituent such as methoxyl, or a strongly electron-abstracting ($-I,-T$) substituent such as the nitro-group. From diazotised *p*-anisidine only a small yield of an intractable tar containing a little azoanisole was obtained; from diazotised *p*-nitroaniline the yield of arylazodiaryl dropped to 0·2% and no 4 : 4′-dinitroazobenzene could be identified, though tarry hydroxyazobenzene derivatives were formed in quantity.

The elucidation of the structures of the azo-compounds obtained from substituted aromatic amines yielded information of considerable interest. Griess (*loc. cit.*) in his account of the reaction between benzenediazonium nitrate and potassium ferrocyanide reported that the solid product, $C_{18}H_{14}N_2$, was mixed with a little azobenzene, which he separated by steam-distillation, and also with a " red oil " of unknown constitution. This red oil was later studied by Ehrenpreis (*Chem. Zentr.*, 1907, I, 1789), who reduced it to a product of m. p. 135—138° which he believed to be triphenylhydrazine, and reported that it gave an acetyl derivative of m. p. 152°. Both Busch and Holbein (*Ber.*, 1907, **40**, 2099) and Wieland and Reverdy (*Ber.*, 1915, **48**, 1112), however, have shown that triphenylhydrazine does not have these properties. Ehrenpreis's compounds may perhaps be semidine derivatives. We have examined further the red oil which remains as the mother-liquor from the crystallisation of 4-phenylazobenzene (I; R = H) from the crude product of the Griess reaction, and have found that on distillation at low pressures it yields a considerable proportion of azobenzene and leaves a residue from which more 4-phenylazobenzene can be separated. We have also attempted to separate chromatographically further components of this oil, and have carried out repeated fractional crystallisations. In consequence of all our work we conclude that it is essentially a mixture of 4-phenylazobenzene with azobenzene, and, in particular, that no appreciable quantities of any isomers of 4-phenylazobenzene are present.

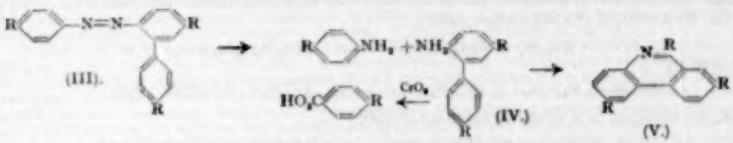
Locher (*loc. cit.*), who carried out the ferrocyanide decomposition with diazotised toluidines and with diazotised α-naphthylamine, reported that *o*-toluidine gave a " *o*-ditolyl-*o*-azotoluene " of m. p. 104°. We have now found that this product separates in a comparatively pure state, in 22% yield, from the reaction mixture together with about 1% of 2 : 2′-azotoluene * and a very little *o*-tolunitrile. Isomers of Locher's product were sought, but none found. The main reaction product has the structure of 4-*o*-tolyl-2 : 2′-azotoluene (I; R = Me) since it could be reduced to a mixture of *o*-toluidine and an aminoditolyl (II). The latter gave *o*-toluic acid on chromic acid oxidation (thus confirming the orientation in ring B), and on bromination at room temperature it gave only a monobromo-derivative, so that the two substituents in ring A must occupy *o*- and *p*-positions to the amino-group. Nitration with copper nitrate and acetic anhydride (Menke, *Rec. Trav. chim.*, 1925, **44**, 141; Waters, *J.*, 1935, 1875) of the acetyl derivative of the base (II), followed by hydrolysis, yielded an *o*-nitro-amine, since it was successfully reduced to a diamine which condensed with phenanthraquinone to give a phenazine derivative. Assuming that the *o*-tolyl configuration is retained

* In the azotoluenes the prefixed numerals refer to the positions of the methyl groups.

in regard to the methyl group in ring A of the base (II), it follows that the original " *o*-ditolyl-*o*-azotoluene " can only have the structure (I).



From diazotised *p*-toluidine Locher isolated a " *p*-ditolyl-*p*-azotoluene " of m. p. 118°; we found that this compound is mixed with small quantities of 4 : 4′-azotoluene and of *p*-tolunitrile, and that it is not accompanied by significant amounts of any isomers. The product is 2-*p*-tolyl-4 : 4′-azotoluene (III; R = Me) since reduction gave *p*-toluidine together with an aminoditolyl (IV; R = Me) which (i) was oxidised to *p*-toluic acid, (ii) yielded only a monobromo-derivative in the cold, and (iii) gave an acetyl derivative which could be condensed to 3 : 7 : 9-trimethylphenanthridine (V; R = Me). Morgan and Walls (*J.*, 1930, 1307) obtained the same amine (IV; R = Me) by pyrolysis of diazoamino-*p*-toluidine and established its structure by conversion into 2 : 6-dimethylcarbazole, which they then synthesised by another route.

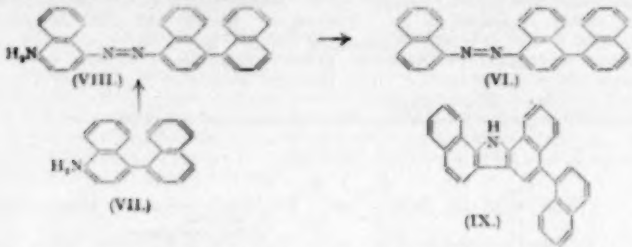


Diazotised *p*-chloroaniline, with which this reaction had not previously been performed, yielded the analogous product, 4 : 4′-*dichloro*-2-p-*chlorophenylazobenzene* (III; R = Cl) with which again the reaction sequence given in the diagram above was successfully carried out. The main reaction product was, in this case, isolated by extraction (Soxhlet) with light petroleum of the bulky brown material which separates from the aqueous reaction mixture. There remains an insoluble residue which exhibits reactions indicative of a polyazo-compound but does not appear to contain isomers of (III). Again, small amounts of 4 : 4′-dichloroazobenzene and of *p*-chlorobenzonitrile were formed. *p*-Nitroaniline gives a similar product [probably (III; R = NO_2)] but only in 0·2% yield. Unfortunately, its structure cannot be established by the same reaction sequence, since reduction would also affect the nitro-groups.

From diazotised α-naphthylamine Locher obtained 1 : 1′-azonaphthalene and another substance. We found that this second compound can be extracted from the solid reaction product in about 9% yield, and it proves to be 4-α-naphthyl-1 : 1′-azonaphthalene (VI). It was synthesised by reducing 4-nitro-1 : 1′-dinaphthyl (Schoepfle, *J. Amer. Chem. Soc.*, 1923, **45**, 1566) to the corresponding *amine* (VII), coupling this with α-naphthylamine and then deaminating the resulting azo-dye (VIII). Reduction of (VI) was also attempted, but the reaction product proved to be 3-α-naphthyl-1 : 2 : 7 : 8-dibenzcarbazole (IX) and not the amine (VII). The production of a dibenzcarbazole derivative affords confirmatory evidence of the structure (VI) of the azo-compound, since carbazole formation can only occur if both β-positions adjacent to the azo-group are unsubstituted.

It will be seen, therefore, that in all these reactions between substituted aromatic diazo-compounds and potassium ferrocyanide an azobenzene derivative is formed in which an aryl residue occupies the *p*-position to the azo-group whenever possible. If this position is blocked in the original amine, the aryl residue occupies the *o*-position to the azo-group. Neither isomers nor symmetrical diarylazodiaryl derivatives appear to be formed. Furthermore, the nitrogen atoms of the substituted bases, $R{\cdot}C_6H_4{\cdot}NH_2$, retain throughout their original

orientations relative to the group R, and the whole distinctive reaction can be viewed as an aromatic substitution by a R·C_6H_4· group.



When this investigation was commenced, it was hoped that the elucidation of the structures of the arylazodiaryls obtainable from substituted aromatic diazo-compounds would help to establish whether the substituting aryl group reacts in the form of a cation or of an electrically neutral radical, but as yet no clear discrimination between plausible alternatives can be made.

Our results show that arylation has occurred in the *p*- or *o*-position to an azo-, or diazo-, group, and not in the *p*- or *o*-position to electron-donating substituents such as Me or Cl. However, since only 1—2% of the simple arylazoaryl compounds could be isolated in comparison with 10—20% of arylazodiaryls, it is improbable that our reaction proceeds by way of arylation of a symmetrical azobenzene derivative, and indeed an attempt to phenylate azobenzene in acetone solution (cf. Part VI, *J.*, 1939, 870) failed. The most probable alternatives therefore require that the diaryl group should be formed at an early stage of the reaction, *i.e.*:

(*a*) By arylation of a diazonium cation:

$$R{\cdot}C_6H_4{\cdot} + (R{\cdot}C_6H_4{\cdot}N_2)^+ \longrightarrow (R{\cdot}C_6H_4{\cdot}C_6H_3R{\cdot}N_2)^+ + H^+$$

followed by

$$(R{\cdot}C_6H_4{\cdot}C_6H_3R{\cdot}N_2)^+ + R{\cdot}C_6H_4{\cdot} + e \longrightarrow R{\cdot}C_6H_4{\cdot}C_6H_3R{\cdot}N{:}N{\cdot}C_6H_4R$$

or (*b*) by arylation of a covalent diazo-hydroxide:

$$R{\cdot}C_6H_4{\cdot} + R{\cdot}C_6H_4{\cdot}N{:}N{\cdot}OH \longrightarrow R{\cdot}C_6H_4{\cdot}C_6H_3R{\cdot}N{:}N{\cdot}OH + H{\cdot}$$

Though the radical-type reactions suggested above seem to afford the best interpretation of our experimental work because of the absence of significant percentages of phenolic products (see p. 834) diagnostic of the presence of aryl cations, we nevertheless cannot exclude entirely cationoid substitutions by aryl ions because the observed *op*-substitution of azo-compounds is characteristic also of reactions involving cationoid attack. Thus 4 : 4′-dichloroazobenzene and 4 : 4′-azotoluene are both nitrated in position 2, adjacent to the ·N:N· group (see Houghton and Waters, *J.*, in the press). We would point out, however, that the simple polar substitution of a benzenediazonium cation, *i.e.*,

$$Ar^+ + (C_6H_4{\cdot}N_2)^+ \longrightarrow \text{products}$$

should give a *m*-substituted product (cf. the nitration of phenyltrimethylammonium salts) and this certainly is not formed.

Experimental.

Preparation of 4-Phenylazobenzene.—Aniline (23 g.), dissolved in hydrochloric acid (82 ml.) and water (50 ml.), was diazotised at 0—5° with sodium nitrite (18 g.) in water (50 ml.), and the resulting solution was buffered with a solution of sodium acetate (100 g.) in water (200 ml.). This cold solution was then added slowly to a stirred solution of potassium ferrocyanide (125 g.) in water (600 ml.) at room temperature. A dark red precipitate of benzenediazonium ferrocyanide formed at once, and decomposed gradually with evolution of nitrogen. The mixture was kept overnight, and the resulting brown solid was then collected, washed thoroughly with water and dilute alkali, and fractionally crystallised from alcohol (charcoal). In this way 4·4 g. (22%) of 4-phenylazobenzene were obtained in the form of orange-yellow crystals, m. p. 152° (Found: C, 83·6; H, 5·3; N, 10·9. Calc. for $C_{18}H_{14}N_2$: C, 83·75; H, 5·4; N, 10·9%). When the benzenediazonium ferrocyanide was separated at once it decomposed to give only a black tar.

The residue from the crystallisation of the 4-phenylazobenzene was a red oil which on distillation at 0·5 mm. pressure yielded 1% of azobenzene and a little more phenylazobenzene.

The aqueous filtrate from the reaction smelt strongly of phenyl isocyanide. On distillation with steam it yielded a little azobenzene but not phenol, and a bulky precipitate of Prussian-blue separated.

When sodium acetate was not added the yield of 4-phenylazobenzene was only about 1%. Neutralisation of the benzenediazonium sulphate or chloride with sodium hydroxide or sodium hydrogen carbonate solutions led to formation of very tarry products.

Reduction of 4-phenylazobenzene with tin and alcoholic hydrochloric acid gave a mixture of aniline and 4-aminodiphenyl; from the latter, 4-acetamidodiphenyl, m. p. and mixed m. p. with an authentic specimen, 167°, was obtained.

4-o-Tolyl-2 : 2′-azotoluene (I; R = Me).—A solution of *o*-toluidine (1 mol.) in ice-cold 20% hydrochloric acid (540 ml., 3 mols.) was diazotised at 0—5° with sodium nitrite solution (75 g. in 200 ml. of water) and the product was buffered with a solution of hydrated sodium acetate (272 g., 2 mols.) in water (225 ml.). The resulting solution was slowly added to a mechanically stirred solution of potassium ferrocyanide (840 g., 2 mols.) in water (3 l.). Nitrogen was evolved gradually. After the mixture had been left overnight, the resulting red precipitate was collected and recrystallised from ethyl alcohol; yield, 22%. The pure product separated in orange-red platelets from methyl alcohol and had m. p. 105·5° (Ehrenpreis gives 104°) (Found: C, 84·2; H, 6·2; N, 9·2. Calc. for $C_{13}H_{12}N_2$: C, 84·0; H, 6·7; N, 9·3%).

The mother-liquors from the recrystallisations were combined, the solvent removed, and the residue distilled in a vacuum. From the combined residues from 5 mols. of *o*-toluidine there were obtained: (i) 0·5 g. of *o*-tolunitrile, b. p. 40°/1·5 mm., identified by hydrolysis to *o*-toluic acid, m. p. and mixed m. p. 103°, and (ii) 5 g. of 2 : 2′-azotoluene, m. p. and mixed m. p. 54°.

Reduction. A solution of the azo-compound (20 g.) in boiling alcohol (500 ml.) was added portionwise to a solution of stannous chloride (112 g. of hydrate) in concentrated hydrochloric acid (112 ml.) at 100°. Each portion was immediately decolorised. (Note. Addition of stannous chloride solution to the azo-compound was unsatisfactory, as it gave an intractable mixture of involatile amines, possibly of semidine type.) The alcohol was removed from the completely reduced solution under diminished pressure, the residue was made strongly alkaline with sodium hydroxide and extracted with ether, and the bases were collected and distilled in a vacuum giving: (i) *o*-toluidine (2·5 g.), identified as its acetyl and benzoyl derivatives, and (ii) 4-amino-3 : 2′-ditolyl (7·1 g.), b. p. 92°/0·005 mm. This was a pale yellow viscous oil which rapidly darkened on storage. Its *acetyl* derivative crystallised from light petroleum (b. p. 60—80°) in fine matted needles, m. p. 143° (Found: C, 80·5; H, 7·22; N, 5·6. $C_{14}H_{11}ON$ requires C, 80·3; H, 7·2; N, 5·8%). Its *dibenzoyl* derivative, prepared by treating the base with an excess of benzoyl chloride in boiling pyridine, crystallised from alcohol in short needles, m. p. 140·5° (Found: C, 83·1; H, 5·7; N, 3·4%; *M* (Rast), 393. $C_{28}H_{21}O_2N$ requires C, 82·9; H, 5·7; N, 3·45%; *M*, 405). Under the same conditions it was found that *N*-dibenzoyl derivatives were obtained from other *o*-substituted amines, including *o*-toluidine itself. The *picrate* of the base crystallised in stout yellow prisms, m. p. 198° (Found: N, 13·2. $C_{26}H_{14}O_7N_4$ requires N, 13·1%).

A portion of the base was oxidised with chromic acid in aqueous acetic acid solution and gave *o*-toluic acid, m. p. and mixed m. p. 102—103°. Another portion (2·0 g.) was dissolved in glacial acetic acid (50 ml.) containing anhydrous sodium acetate (2·5 g.) and a 3% solution of bromine in glacial acetic acid was added dropwise. When just over one molar equiv. (60 ml.) had been added free bromine remained in the solution. To ensure completion of the reaction a slight further excess of bromine was added, and after 5 minutes the mixture was poured into dilute alkaline sodium sulphite solution. The purple oily 5-bromo-4-amino-3 : 2′-ditolyl was collected. From a small part the *hydrochloride* was prepared and crystallised from alcoholic hydrochloric acid in glistening needles, m. p. 160° (decomp.) (Found: Cl + Br, 34·4. $C_{14}H_{14}NBr,HCl$ requires Cl + Br, 36·8%). The remainder was benzoylated as described above, and yielded *5-bromo-4-dibenzamido-3 : 2′-ditolyl*, which crystallised from alcohol in rosettes of needles, m. p. 175° (Found: C, 69·4, 69·3*; H, 4·8, 4·7*; N, 3·0%; *M*, 485. $C_{28}H_{20}O_2NBr$ requires C, 69·5; H, 4·6; N, 2·9%; *M*, 484) (* denotes macro-analysis by Mr. F. C. Hall).

Nitration of 4-Acetamido-3 : 2′-ditolyl.—Powdered hydrated copper nitrate (7 g.) was added in small portions to a stirred suspension of acetamidoditolyl (10·5 g.) in acetic anhydride (50 ml.), kept at 25—30° in a bath of cold water. After an hour the clear green solution was poured into water, and the pale yellow *5-nitro-4-acetamido-3 : 2′-ditolyl* (90%) was collected and hydrolysed by refluxing for 6 hours with a 30% solution of sulphuric acid in ethyl alcohol. After removal of the alcohol, the residue was poured into water and the resulting *5-nitro-4-amino-3 : 2′-ditolyl* was crystallised repeatedly from aqueous methyl alcohol. It formed long orange needles, m. p. 95° (Found: C, 69·3; H, 5·9; N, 11·5. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8; N, 11·6%).

This base (0·5 g.) was reduced with an excess of zinc dust in boiling glacial acetic acid solution (25 ml.), and the purple solution was filtered into a solution of phenanthraquinone (0·4 g.) in hot glacial acetic acid (10 ml.). After the mixture had been heated for an hour it was poured into water, and a black powder separated. This was dissolved in acetone and passed down a column of activated alumina. On precipitation with water the eluted liquid gave a brown powder which was collected and crystallised repeatedly from benzene–light petroleum (b. p. 40—60°), to give eventually *12-o-tolyl-10-methylphenanthrarine* (*8-o-tolyl-6-methyl-1 : 2 : 3 : 4-dibenzphenarine*) as very small light-brown needles, m. p. 192—193° (Found: C, 86·9; H, 5·0; N, 7·2. $C_{21}H_{15}N$ requires C, 87·4; H, 5·2; N, 7·3%). This substance gave a brilliant purple solution in concentrated sulphuric acid.

2-p-Tolyl-4 : 4′-azotoluene.—A diazotised solution of *p*-toluidine (1 mol.) was buffered with sodium acetate, as described above, and added slowly with stirring to a solution of potassium ferrocyanide (1 mol.) in water (1½ l.). A red diazonium ferrocyanide was precipitated, but quickly decomposed with evolution of nitrogen, leaving a dark brown solid and an aqueous liquid which did not react with alkaline β-naphthol. The solid (yield, 55—60%) was collected and extracted with hot alcohol. The tarry product was crystallised repeatedly from light petroleum (b. p. 60—80°) and then alcohol, to give pure *2-p-tolyl-4 : 4′-azotoluene* in 10% yield, together with a much smaller amount of 4 : 4′-azotoluene, m. p. and mixed m. p. 142°. Attempts to isolate other products from the residual tar were not successful. The main product had m. p. 118°, in agreement with Ehrenpreis (Found: C, 83·7; H, 6·7; N, 9·6. Calc. for $C_{13}H_{12}N_2$: C, 84·0; H, 6·7; N, 9·3%).

The azo-compound was reduced with stannous chloride in alcoholic hydrochloric acid, and, after

removal of the excess of alcohol, the solution was made alkaline and distilled in steam. *p*-Toluidine collected in the receiver as a white solid; its identity was confirmed. The remaining liquid was cooled, extracted with ether, and the **2-*amino*-5 : 4'-*ditolyl*** which had been formed was finally purified by distillation in a vacuum (b. p. 123—128°/0·4 mm.) (Found: C, 85·2; H, 7·6; N, 7·5. $C_{14}H_{15}N$ requires C, 85·3; H, 7·6; N, 7·1%). Its acetyl derivative crystallised from aqueous alcohol in long needles, m. p. 104° (Found: C, 80·3; H, 7·1; N, 5·6. Calc. for $C_{14}H_{17}ON$: C, 80·3; H, 7·1; N, 5·9%), and its *benzoyl* derivative formed white needles, m. p. 122° (Found: C, 83·4; H, 6·5; N, 4·8. $C_{21}H_{19}ON$ requires C, 83·7; H, 6·3; N, 4·7%). On treatment for 20 minutes with concentrated nitric acid, the acetyl derivative yielded a dinitro-compound, probably **3 : 2'-*dinitro*-2-*acetamido*-5 : 4'-*ditolyl***, which crystallised from very dilute alcohol in yellow needles, m. p. 191° (Found: C, 58·7; H, 4·8; N, 13·0. $C_{16}H_{15}O_5N_3$ requires C, 58·4; H, 4·6; N, 12·8%).

On oxidation with chromic acid in aqueous acetic acid the 2-amino-5 : 4'-ditolyl (1 g.) gave *p*-toluic acid (0·2 g.), m. p. and mixed m. p. 177°.

3-*Bromo*-2-*amino*-5 : 4'-*ditolyl*.—2-Amino-5 : 4'-ditolyl (1 g.) was dissolved in carbon tetrachloride (20 ml.), a little powdered sodium acetate was added, and a 1% solution of bromine in carbon tetrachloride was slowly run into the mixture, cooled in ice. When excess of bromine was present, aqueous sulphurous acid was immediately stirred in to prevent further conversion into dark products. The carbon tetrachloride layer after separation, washing with water, and evaporation gave a dark residue from which white crystals of the *bromo*-base were obtained by crystallisation from aqueous methyl alcohol (charcoal); m. p. 68° (Found: C, 60·7; H, 5·1; Br, 28·8. $C_{14}H_{14}NBr$ requires C, 60·9; H, 5·1; Br, 28·9%). Its *acetyl* derivative crystallised from aqueous alcohol in white needles, m. p. 135° (Found: C, 60·2; H, 4·9. $C_{16}H_{16}ONBr$ requires C, 60·4; H, 5·0%), and its *monobenzoyl* derivative, prepared by the Schotten–Baumann method, formed white needles, m. p. 195° (Found: C, 66·0; H, 4·6. $C_{21}H_{18}ONBr$ requires C, 66·5; H, 4·5%).

3 : 7 : 9-*Trimethylphenanthridine*.—2-Acetamido-5 : 4'-ditolyl (1·3 g.) and phosphorus oxychloride (3 g.) were heated under reflux in nitrobenzene solution (15 ml.) with the addition of a drop of stannic chloride as catalyst. After 4 hours the evolution of hydrogen chloride had ceased. The mixture was then poured into water, nitrobenzene was removed by distillation in steam, and the remaining solid, consisting of the hydrochloride of 3 : 7 : 9-trimethylphenanthridine, was collected and crystallised from alcohol containing a little hydrochloric acid. It formed pale yellow felted needles which did not melt below 250°. The free *base* was prepared from this and purified by crystallisation from light petroleum (b. p. 60—80°); yield, 60%. It formed pale yellow prisms, m. p. 123° (Found: C, 87·0; H, 6·8; N, 6·4. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%).

4 : 4'-*Dichloro*-2-p-*chlorophenylazobenzene* (III; R = Cl).—*p*-Chloroaniline (42·5 g., 0·33 mol.) in 25% hydrochloric acid (150 ml., 1 mol.) was diazotised below 5°, buffered with sodium acetate (91 g., 0·66 mol.) in water (75 ml.), and slowly added, with mechanical stirring, to a solution of potassium ferrocyanide (280 g., 0·66 mol.) in water (1 l.). Evolution of nitrogen was immediate and rapid and a few drops of butyl alcohol had to be added to control foaming. After the mixture had been left overnight, the light-brown precipitate was collected, dried (yield, 60%), and extracted thoroughly with light petroleum (b. p. 60—80°). A yellow crystalline solid was obtained, together with tar. By repeated crystallisation from acetic acid and then acetone the former gave, in 13% yield, pale yellow felted needles of **4 : 4'-*dichloro*-2-p-*chlorophenylazobenzene***, m. p. 153° (Found: C, 60·2; 59·9; H, 3·2, 3·3; N, 7·8, 7·6; Cl, 29·4. $C_{18}H_{11}N_2Cl_3$ requires C, 59·8; H, 3·0; N, 7·8; Cl, 29·5%). The red tarry residue was evaporated and distilled in a vacuum. It gave a trace of *p*-chlorobenzonitrile, and then, at 120—170°/0·5 mm., an orange oil which solidified, and gave, on recrystallisation, orange needles of 4 : 4'-dichloroazobenzene (1%), m. p. and mixed m. p. 183°. Steam-distillation of the aqueous liquid from the initial reaction gave a further small quantity of *p*-chlorobenzonitrile, identified by hydrolysis to *p*-chlorobenzoic acid, m. p. and mixed m. p. 232°.

Reduction. 4 : 4'-Dichloro-2-*p*-chlorophenylazobenzene (10 g.) in boiling glacial acetic acid was treated, in portions, with zinc dust (15 g.). To complete the reduction a mixture of hydrochloric acid (5 ml.) in acetic acid (20 ml.) was subsequently added. The colourless solution was filtered hot, concentrated, and made strongly alkaline with 50% sodium hydroxide solution. The bases were extracted with ether, this solvent was removed, and the residue was extracted at 80° with five successive portions of hot water. The aqueous extract, on cooling, deposited *p*-chloroaniline (0·8 g.), identified by its acetyl and benzoyl derivatives (m. p.s and mixed m. p.s with authentic specimens 177° and 191°, respectively). The residue was a sticky product, and, since attempts at crystallisation failed, it was benzoylated in pyridine solution, and the benzoylated amines were fractionally crystallised from aqueous alcohol. **5 : 4'-*Dichloro*-2-*benzamidodiphenyl*** (2 g.) was thus obtained in white needles, m. p. 191° (Found: C, 66·7; H, 4·4; N, 4·0. $C_{19}H_{13}ONCl_2$ requires C, 66·7; H, 3·8; N, 4·1%) (C and H analysis by Mr. G. Ingram).

A small portion of the crude base was oxidised with chromic acid in acetic acid solution and gave *p*-chlorobenzoic acid, m. p. and mixed m. p. 232° (anilide, m. p. 195°).

3 : 7-*Dichloro*-9-*phenylphenanthridine*.—3 : 4'-Dichloro-2-benzamidodiphenyl (1 g.) and phosphorus oxychloride (3 g.) were heated under reflux for 6 hours in nitrobenzene solution (10 ml.) together with a few drops of stannic chloride. A further ml. of phosphorus oxychloride was then added, and the heating continued for another 10 hours. The product was poured into water and steam-distilled, and the solid residue was collected and recrystallised from alcoholic hydrochloric acid, yielding pale yellow needles of the hydrochloride of the phenanthridine. The free *base*, obtained by treating the salt with aqueous ammonia and extraction with ether, crystallised from benzene in colourless needles, m. p. 193°, not identical with those of the original dichlorobenzamidodiphenyl (m. p. 191°); yield, 50% (Found: C, 69·9; H, 3·6; N, 4·4. $C_{19}H_{11}NCl_2$ requires C, 70·4; H, 3·4; N, 4·3%) (C and H analysis by Mr. G. Ingram). This base gave a *picrate*, which crystallised from benzene in mustard-yellow needles, m. p. 220° (Found: N, 9·9. $C_{25}H_{14}O_7N_4Cl_2$ requires N, 10·1%). The ultra-violet absorption spectrum of the base in methyl-alcoholic solution (maxima at 2600, 3410, and 3575 A.) accorded with the phenanthridine structure.

4 : 4′-*Dinitro*-2-*p*-*nitrophenylazobenzene*.—*p*-Nitroaniline (46 g.) and sodium nitrite (25 g.) were ground to a smooth paste with water (100 ml.) and poured on a mixture of ice (100 g.) and concentrated hydrochloric acid (100 ml.). After being stirred for 10 minutes, the mixture was filtered into a solution of sodium acetate (91 g.) in water (100 ml.), and the product was slowly added to a mechanically stirred solution of potassium ferrocyanide (280 g.) in water (1 l.). A few drops of butyl alcohol were added to moderate the foaming which occurred. After the mixture had been left overnight, the black precipitate was collected, dried, and extracted with absolute alcohol (Soxhlet). The alcohol was then removed, the residue was boiled with 10% sodium hydroxide solution to remove hydroxyazo-compounds, and the alkali-insoluble residue was crystallised repeatedly from acetone and then from xylene. It gave the **4 : 4′-*dinitro*-2-*p*-*nitrophenylazobenzene*** as a brick-red powder, m. p. 240° (decomp.) (yield, ¼%) (Found : N, 18·0. $C_{18}H_{11}O_6N_5$ requires N, 17·6%). In admixture with authentic 4 : 4′-dinitroazobenzene (m. p. 219°) (Calc. : N, 20·6%) the m. p. was lowered to 203°. When this was boiled with alcoholic ammonium sulphide and the product made strongly alkaline, an intense grass-green colour was produced. Under the same conditions 4 : 4′-dinitroazobenzene gave an intense blue colour.

The reaction described above for *p*-toluidine was repeated with *p*-anisidine. The product was a sticky tar from which by repeated crystallisation from methyl alcohol, yellow 4 : 4′-azoanisole, m. p. and mixed m. p. 158—159°, was eventually isolated in ½% yield, together with anisonitrile, m. p. 46°, in ½% yield.

4-α-*Naphthyl*-1 : 1′-*azonaphthalene* (VI).—α-Naphthylamine (143 g., 1 mol.) was dissolved in hot 20% hydrochloric acid (500 ml.), cooled rapidly, and diazotised with aqueous sodium nitrite (58 g.). The diazotised solution was buffered with sodium acetate (300 g.) in water (250 ml.) and then added gradually to a stirred solution of potassium ferrocyanide (928 g., 2 mols.) in water (2 l.). The evolution of nitrogen was immediate and rapid, and it was necessary to add drops of butyl alcohol to prevent foaming. After being left overnight, the brown precipitate was collected, dried (yield, 85%), and extracted for 2 days (Soxhlet) with light petroleum (b. p. 60—80°). The extract was concentrated to 250 ml., and the solid product, which contained much tar, was boiled with benzene, with the addition of charcoal (5 g.). This solution deposited a brown solid which, by successive crystallisations from alcohol, light petroleum (b. p. 60—80°), glacial acetic acid, and finally acetone, gave, in 9% yield, brick-red microscopic needles of **4-α-*naphthyl*-1 : 1′-*azonaphthalene***, m. p. 178° (Found : C, 87·3; H, 4·8; N, 6·9. $C_{20}H_{14}N_2$ requires C, 88·2; H, 4·9; N, 6·9%). This was also synthesised as follows.

4-Nitro-1 : 1′-dinaphthyl (Schoepfle, *loc. cit.*) (10 g.) in boiling alcohol (200 ml.) was treated with a solution of stannous chloride (45 g.) in concentrated hydrochloric acid (40 ml.). After refluxing for 1 hour the alcohol was removed, and the residue poured into 30% sodium hydroxide (300 ml.). The crude **4-*amino*-1 : 1′-*dinaphthyl*** was collected, extracted with ether, and finally crystallised from alcohol. It formed pink nodules, m. p. 157—158° (8 g.) (Found : C, 89·3; H, 5·6; N, 5·4. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6; N, 5·2%). Its *acetyl* derivative crystallised from aqueous pyridine in small white plates, m. p. 256·5° (Found : C, 84·4; H, 5·6; N, 4·6. $C_{22}H_{17}ON$ requires C, 84·9; H, 5·6; N, 4·5%), and its *dibenzoyl* derivative had m. p. 210° (Found : C, 85·9; H, 5·2. $C_{34}H_{23}O_2N$ requires C, 85·5; H, 4·9%).

The above base (7 g.) was diazotised in hydrochloric acid suspension. After 20 minutes, excess of nitrous acid was removed with urea (5 g.) and a solution of α-naphthylamine (4 g.) in glacial acetic acid (35 ml.) was added, followed by 30% sodium hydroxide solution (150 ml.). The reddish-brown aminoazo-compound was allowed to settle overnight and then was collected and dried : m. p. ca. 160° (decomp.); yield, quantitative (12 g.). It was dissolved in a mixture of alcohol (100 ml.) and concentrated sulphuric acid (5·4 g.) and treated at 0° with freshly prepared amyl nitrite (3·8 g.). After being kept for 12 hours at room temperature, the mixture was slowly warmed, and finally it was refluxed for an hour. Water was then added, the alcohols were removed under diminished pressure, and the residual black tar was washed with water and extracted with boiling alcohol. The extract, on precipitation with water, gave a bright red solid which was redissolved in 80% alcohol and passed down an alumina column, which retained both tar and azo-dye. The eluted material was repeatedly crystallised from acetone and glacial acetic acid alternately, and finally gave **4-α-naphthyl-1 : 1′-azo-naphthalene** as dark red granules, m. p. 178—179° not depressed on admixture with the product obtained as before. When crushed, the granules gave a brick-red powder.

Reduction of **4-α-*Naphthyl*-1 : 1′-*azonaphthalene***.—A boiling solution of the azo-compound (10 g.) in glacial acetic acid (200 ml.) was reduced by gradual addition of zinc dust (20 g.), hydrochloric acid (5 ml.) being added to complete the reaction. After filtration, the product was concentrated and treated with a large excess of 50% sodium hydroxide solution; ammonia was then evolved. The resulting solid was collected on sintered glass. No part of it was volatile in steam, and consequently α-naphthylamine was not present. The solid was purified by dissolution in alcohol and partial precipitation with water until a product was obtained which could be recrystallised from benzene–light petroleum (b. p. 40—60°). This was **3-α-*naphthyl*-1 : 2 : 7 : 8-*dibenzcarbazole*** (IX), m. p. 218—219°; yield 55% (Found : C, 90·8; H, 4·8; N, 3·4. $C_{28}H_{17}N$ requires C, 91·6; H, 4·9; N, 3·6%). On crystallisation from absolute alcohol it gave brownish-yellow needles of an alcohol complex, which decomposed when heated to 136° to give the free carbazole.

The *picrate* of the carbazole derivative crystallised in maroon-coloured plates, sintering at 246° and melting at 252° (decomp.) (Found : N, 7·9. $C_{34}H_{20}O_7N_4$ requires N, 9·0%).

The carbazole in dilute alcoholic solution showed an intense blue-green fluorescence in ultra-violet light. It gave a pale red solution in concentrated sulphuric acid, which became intense indigo-blue on treatment with many oxidising agents (HNO_2, $K_2Cr_2O_7$, $K_2S_2O_8$, $FeCl_3$, V_2O_5).

Attempted Phenylation of Azobenzene.—Solid zinc benzenediazonium chloride, $(PhN_2Cl)_2,ZnCl_2$, from 18 g. of aniline, was added to a solution of azobenzene (15 g.) in dry acetone (200 ml.) containing suspended calcium carbonate (20 g.), and zinc dust (10 g.) was then added in portions with vigorous shaking. Nitrogen was evolved steadily. On the following day the mixture was heated to boiling and filtered, and the residue was washed with hot acetone. The solution on evaporation gave a brown syrup which was extracted with hot alcohol. From this extract only a brown sludge could be obtained.

Extraction of the latter with light petroleum (b. p. 60—80°), followed by repeated crystallisation, eventually led to the recovery of about 50 mg. of unchanged azobenzene; no other crystalline product could be separated.

Except where otherwise stated, all analyses are by Drs. Strauss and Weiler. M. p.s are uncorrected.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, December* 15*th*, 1949.]

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169. *The Synthesis of Thyroxine and Related Substances. Part VI. The Preparation of Some Derivatives of* DL-*Thyroxine.*

By J. C. CLAYTON and B. A. HEMS.

A number of new derivatives of DL-thyroxine have been prepared; their solubilities and physiological activities are recorded. A new method of iodination of 3 : 5-di-iodothyronine and its derivatives is described.

IN the introduction to this series (Borrows, Clayton, and Hems, *J.*, 1949, S 185) it was stated that one of the aims of the work was to prepare derivatives of thyroxine that would be suitable for oral administration in the treatment of hypothyroidism. It was generally thought at that time (Harington, "The Thyroid Gland," London, 1933) that free thyroxine was ineffective orally, presumably because of its low solubility and consequent poor absorption from the gut. If that were so a soluble derivative might be more useful. We have prepared certain new derivatives of thyroxine; values have been obtained for their solubilities and physiological potencies, and are shown in the Table. Thyroxine methyl ester is included

Substance.	Activity.	Solubility in water, (g./100 ml. at 25°).
DL-Thyroxine monosodium salt	1·0	<0·001 pH 7·0
Thyroxine methyl ester	0·65	0·017 pH 7·6
Thyroxine ethyl ester	0·5	0·002 pH 7·6
N-Formylthyroxine	0·3	0·16 pH 7·3 0·37 pH 9·2
N-Phthaloylthyroxine	inactive	<0·02 pH 7·6
N-β-Carboxypropionylthyroxine	0·07	0·95 pH 7·6
N-Oxalothyroxine	0·3	0·14 pH 7·6
O-Carboxymethylthyroxine	0·1	0·03 pH 7·6
N-Carbamylthyroxine sodium salt	inactive	0·6 pH 7·0
Thyroxine methyl ether	0·5	<0·008 pH 7·6

since no figure for its activity has been reported. The biological activities of these compounds were determined by injection into mice, using the method devised by Smith, Emmens, and Parkes (*J. Endocrinol.*, 1947, **5**, 186).

Thyroxine ethyl ester hydrochloride was prepared by treating with hydrogen chloride a suspension of the amino-acid in ethyl alcohol: it was converted into the *ethyl* ester by treatment with the equivalent quantity of sodium hydroxide solution. *N-Formylthyroxine* was prepared by heating the amino-acid with formic acid under reflux, and *N-phthaloylthyroxine* was obtained by treatment of thyroxine with phthalic anhydride at 180° according to Billmann and Harting's general method (*J. Amer. Chem. Soc.*, 1948, **70**, 1473). For other *N*-acyl derivatives the methyl ester of thyroxine in anisole solution was treated with the appropriate acid chloride and the *N*-acyl esters were then hydrolysed with sodium hydroxide solution (cf. Ashley and Harington, *Biochem. J.*, 1928, **22**, 1436). Thus, N-β-*carboxypropionylthyroxine* and *N-oxalothyroxine* were prepared from thyroxine methyl ester and β-carbethoxypropionyl chloride and methoxalyl chloride, respectively.

When thyroxine was heated under reflux with 2N-sodium hydroxide solution and chloroacetic acid, the substance obtained on acidification appeared to be *O-carboxymethylthyroxine*, since it showed a positive ninhydrin reaction, but no colour with sodium nitrite in acid solution followed by basification with ammonia, a test in which 2 : 6-di-iodophenols give a red colour (Kendall and Osterberg, *J. Biol. Chem.*, 1919, **40**, 265; Harington and Barger, *Biochem. J.*, 1927, **21**, 169). Furthermore, electrometric titration demonstrated the presence of one basic group and only two acidic groups.

The monosodium salt of *N-carbamylthyroxine* was prepared by heating the sodium salt of thyroxine with an aqueous solution of sodium cyanate. Attempts to prepare the free hydantoic acid from the sodium salt failed, since rapid cyclisation to *thyroxinehydantoin* took place. This

last compound was characterised by catalytic hydrogenolysis, the product proving identical with *thyroninehydantoin* prepared from thyronine by the usual method.

There is some doubt about the activity of thyroxine methyl ether, which has been prepared by two different methods. One was the action of diazomethane on thyroxine, followed by hydrolysis of the resultant ester (Loeser, U.S.P. 2,252,230); the product was reported to melt at 226—228° and was claimed to be highly active. In the other, *N*-acetylthyroxine was methylated with methyl sulphate, and the acetyl group was subsequently removed by hydrolysis (Myers, *Proc. Staff Meetings, Mayo Clinic*, 1932, **7**, 201; *J. Amer. Chem. Soc.*, 1932, **54**, 3718). The product melted at 210—213° and was said to be active when administered to tadpoles, but had no effect upon normal men. Difficulties were encountered in attempting to follow Myers's intructions and no methyl ether was obtained. Consequently, thyroxine methyl ether was prepared by Loeser's procedure and identified as the methyl ether by hydrogenolysis to a compound that proved identical with an authentic specimen of *thyronine methyl ether*; this was prepared by hydrolysis and simultaneous racemisation of **3** : 5-di-iodo-4-*p*-methoxyphenoxy-*N*-acetyl-L-phenylalanine ethyl ester to **3** : 5-*di-iodo*-4-*p*-*methoxyphenoxy*-DL-*phenylalanine*, which was then hydrogenolysed.

In preparing thyroxine by the iodination of **3** : 5-di-iodothyronine in strong aqueous ammonia (Harington and Barger, *loc. cit.*; Harington, *Biochem. J.*, 1928, **22**, 1429) trouble was often encountered through the formation of explosive nitrogen iodides. By careful working, in particular by adding the iodine solution slowly below the surface of the liquid, the formation of nitrogen iodides was avoided, but the method was thought to involve an undesirable risk, particularly in larger scale preparations. To avoid this risk several other known methods of iodination were attempted, but none was satisfactory. Finally it was thought that solutions of organic bases might be useful as solvents, since their iodine derivatives are known to be non-explosive. The use of tertiary bases met with no success, but aqueous or alcoholic solutions of primary or secondary aliphatic bases proved to be very suitable media for iodination. **3** : 5-Di-iodothyronine is much more soluble in these solutions than in aqueous ammonia, and the iodination appeared to proceed more rapidly, although detailed studies on this point have not been carried out. The method is simple and convenient and thyroxine is obtained consistently in 90% yield. Several primary and secondary aliphatic bases have been used and aqueous ethylamine solutions have proved to be generally useful. The method has also been used in the iodination of derivatives of **3** : 5-di-iodothyronine, *N*-formyl- (Harington, *loc. cit.*), *N-acetyl-*, and N-β-*carboxypropionyl*-**3** : 5-*di-iodothyronine*, giving the corresponding thyroxine derivatives in good yield. Similarly, **3** : 5-*di-iodothyroninehydantoin* could be iodinated to thyroxinehydantoin, which proved to be identical with the compound prepared by cyclisation of *N*-carbamylthyroxine.

Although iodination of **3** : 5-di-iodothyronine methyl ester did take place in aqueous solutions of bases, the compound underwent hydrolysis and thyroxine was the sole product. However, under anhydrous conditions, for example, using methyl alcohol and *n*-butylamine as the solvent, thyroxine methyl ester was readily obtained.

Experimental.

Thyroxine Ethyl Ester.—Hydrogen chloride was passed into a mixture of thyroxine (1 g.) and ethyl alcohol (10 ml.), and the solid rapidly went into solution. When the solution was saturated it was allowed to cool and was re-treated with hydrogen chloride. Evaporation yielded a solid residue of the ester hydrochloride (0·97 g.) which was dissolved in aqueous ethyl alcohol; one equivalent of *N*-sodium hydroxide was then added. The *ethyl* ester was precipitated as a white solid and was filtered off, washed, and dried. It (0·7 g.) had m. p. 156—157° (Found: C, 26·0; H, 1·8; N, 1·75; I, 62·55. $C_{17}H_{15}O_4NI_4$ requires C, 25·4; H, 1·9; N, 1·7; I, 63·1%).

N-Formylthyroxine.—Thyroxine (1 g.) was heated under reflux with formic acid (12 ml.; 98—100%) for five hours, and the solution cooled and evaporated *in vacuo* to dryness. The residue was heated for 1·5 hours with more formic acid (10 ml.), and the solution evaporated. The product was completely soluble in dry acetone from which it crystallised on addition of water. The material was recrystallised from aqueous acetone and the *N-formyl* compound separated as a white powder, m. p. 223° (decomp.) (Found: C, 25·2; H, 1·8; N, 1·6; I, 62·0. $C_{16}H_{11}O_4NI_4,\frac{1}{2}C_3H_6O$ requires C, 24·75; H, 1·6; N, 1·7; I, 61·7%).

N-Phthaloylthyroxine.—A mixture of thyroxine (0·5 g.) and phthalic anhydride (0·4 g.) was heated in a test-tube to 180°, by means of an oil-bath. The bath was maintained at this temperature for fifteen minutes. The solid slowly melted to a homogeneous brown liquid. After cooling, the solidified mass was extracted with boiling glacial acetic acid, and the solid obtained on cooling was recrystallised from ethyl acetate–light petroleum (b. p. 80—100°) as white prisms (0·3 g.), m. p. 156—157° (decomp.) (Found: C, 30·7; H, 1·8; N, 1·5. $C_{24}H_{13}O_6NI_4$ requires C, 30·45; H, 1·4; N, 1·5%).

N-β-Carboxypropionylthyroxine.—To a solution of thyroxine methyl ester (Ashley and Harington, *Biochem. J.*, 1928, **22**, 1436) (1 g.) in anisole (40 ml.) cooled to 0°, a solution of β-carbethoxypropionyl

chloride (0·14 g.) (Papa, Schwenk, and Hankin, *J. Amer. Chem. Soc.*, 1947, **69**, 3018) in anisole (2 ml.) was added. After one hour the precipitate was filtered off and identified by m. p. and mixed m. p. as thyroxine methyl ester hydrochloride (0·55 g.). The filtrate was evaporated to dryness *in vacuo* and the residue dissolved in benzene. After a short time white prisms (0·4 g.), m. p. 139—141°, were deposited, and were identified by analysis as *N-β-carbethoxypropionylthyroxine methyl ester* (Found: C, 29·1; H, 2·7; N, 1·4; I, 56·6. $C_{22}H_{21}O_7NI_4$ requires C, 28·7; H, 2·3; N, 1·5; I, 55·3%).

The ester was dissolved in ethyl alcohol (5 ml.) containing N-sodium hydroxide (4 ml.). After one hour at room temperature, N-hydrochloric acid (4 ml.) was added to precipitate the *N-β-carboxypropionylthyroxine*. This crystallised from aqueous alcohol as white prisms (0·25 g.), m. p. 202—203° (decomp.) (Found: C, 25·9; H, 1·5; N, 1·4; I, 57·5. $C_{18}H_{13}O_7NI_4$ requires C, 26·0; H, 1·7; N, 1·6; I, 58·0%).

N-Oxalothyroxine.—In a similar manner *N-oxalothyroxine* was prepared from thyroxine methyl ester and methoxalyl chloride; it crystallised from alcoholic alkali, on addition of acetic acid, as a white powder, m. p. 225—226° (decomp.) (Found: C, 24·2; H, 1·7; N, 1·6; I, 62·4. $C_{17}H_{11}O_7NI_4$ requires C, 24·05; H, 1·3; N, 1·65; I, 59·8%).

O-Carboxymethylthyroxine.—To thyroxine (1 g.) in water (30 ml.) containing N-sodium hydroxide (6 ml.) chloroacetic acid (0·12 g.) was added, and the mixture was boiled under reflux for two hours. An equal volume of alcohol was added and the mixture was treated with charcoal and filtered, and the pH adjusted to 5 by addition of glacial acetic acid. On cooling, silvery plates were deposited which were recrystallised by solution in alcoholic alkali and addition of acetic acid. *O-Carboxymethylthyroxine* (0·7 g.) had m. p. 208—209° (decomp.) (Found: C, 24·2; H, 2·1; N, 1·6; I, 60·1. $C_{17}H_{13}O_6NI_4$ requires C, 24·4; H, 1·6; N, 1·7; I, 60·9%).

Sodium Salt of N-Carbamylthyroxine.—Thyroxine monosodium salt (1 g.) suspended in water (75 ml.) containing sodium cyanate (0·4 g.) was heated under reflux for one hour and then an aqueous solution (25 ml.) of sodium cyanate (0·4 g.) was added and heating continued for three hours. The clear solution was concentrated *in vacuo* to 50 ml. and kept in the ice-chest whereupon the *sodium* salt separated as a white powder (0·7 g.). It was purified by dissolution in methyl alcohol (10 ml.) and addition of ether (100 ml.) whereupon a white solid was obtained (Found: N, 3·3; I, 59·5; Na, 2·9. $C_{16}H_{11}O_4N_2I_4Na$ requires, N, 3·3; I, 60·3; Na, 2·7%).

5-[3 : 5-Di-iodo-4-(3 : 5-di-iodo-4-hydroxyphenoxy)benzyl]hydantoin.—To a suspension of thyroxine monosodium salt (0·8 g.) in water (75 ml.) 0·2N-sodium hydroxide (8 ml.) and sodium cyanate (0·4 g.) were added and the solution was heated under reflux for 2·5 hours. Concentrated hydrochloric acid (40 ml.) was added, and heating was continued for one hour. After cooling, the *hydantoin* was filtered off and recrystallised from acetic acid from which it separated as white prisms (0·73 g.), softening at 169—170° and decomposing at 235° (Found: C, 25·4; H, 1·6; N, 3·4. $C_{18}H_{10}O_4N_2I_4,C_2H_4O_2$ requires C, 25·1; H, 1·6; N, 3·25%).

5-(4-p-Hydroxyphenoxybenzyl)hydantoin.—(*a*) A suspension of thyronine (2 g.) in water (20 ml.) containing sodium cyanate (1 g.) was refluxed until all solid had dissolved. Concentrated hydrochloric acid (12 ml.) was added and the mixture was heated under reflux for a further 30 minutes. The solid obtained on cooling was filtered off and recrystallised from aqueous acetic acid from which the *hydantoin* separated as colourless feathery clusters (1·9 g.), m. p. 256—257° (decomp.) (Found: C, 64·0; H, 4·8; N, 9·3. $C_{16}H_{14}O_4N_2$ requires C, 64·4; H, 4·7; N, 9·4%).

(*b*) 5-[3 : 5-Di-iodo-4-(3 : 5-di-iodo-4-hydroxyphenoxy)benzyl]hydantoin (0·17 g.) was hydrogenolysed in 0·1N-sodium hydroxide solution (20 ml.) using palladised calcium carbonate (0·5 g.) as catalyst. The crude product was crystallised from aqueous acetic acid and proved identical [m. p. and mixed m. p. 256—257° (decomp.)] with a specimen of the material obtained in (*a*) above (yield, 0·055 g.).

Thyroxine Methyl Ether.—This compound was prepared from thyroxine methyl ester by treatment with diazomethane and hydrolysis (Loeser, U.S.P. 2,252,230). It had m. p. 224—225° (decomp.).

3 : *5-Di-iodo-4-p-methoxyphenoxy-*DL*-phenylalanine*.—A mixture of **3** : 5-di-iodo-4-*p*-methoxyphenoxy-*N*-acetyl-L-phenylalanine ethyl ester (see Part V, *J.*, 1949, 3424) (2 g.) and 2N-sodium hydroxide solution (30 ml.) was heated under reflux for 24 hours. To the cooled solution, acetic acid was added whereupon a white solid was deposited. This was filtered off and recrystallised from 50% aqueous acetic acid, from which the *phenylalanine* separated as white prisms, m. p. 238—239° (decomp.) (Found: N, 2·3; I, 46·9. $C_{16}H_{15}O_4NI_2$ requires N, 2·6; I, 47·1%).

Thyronine Methyl Ether.—(*a*) A solution of **3** : 5-di-iodo-4-*p*-methoxyphenoxyphenylalanine (0·6 g.) in ethyl alcohol (10 ml.) and 2N-sodium hydroxide (10 ml.) was shaken in hydrogen with palladised calcium carbonate (0·5 g.) until the uptake of hydrogen was complete. The filtered solution was acidified with acetic acid and, on storage, colourless needles of *thyronine methyl ether* separated and were crystallised from aqueous ethyl alcohol. This ether had m. p. 248° (decomp.) (Found: C, 66·8; H, 6·2; N, 5·0. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9; N, 4·9%).

(*b*) A solution of thyroxine methyl ether (0·4 g.) in ethyl alcohol (8 ml.) and 2N-sodium hydroxide (8 ml.) was shaken in hydrogen with palladised calcium carbonate (0·5 g.) until hydrogenolysis was complete. The solution was filtered and acidified with acetic acid; a white solid, m. p. 246° (decomp.) undepressed on admixture with a sample of thyronine methyl ether from (*a*) above, was precipitated.

Iodination of **3** : *5-Di-iodothyronine and Its Derivatives*.—*Thyroxine*. To a stirred solution of **3** : 5-di-iodothyronine (2 g.) in aqueous ethylamine solution (20 ml.; 20%) a solution of iodine in potassium iodide solution (8·2 ml.; 1·85N.) was added dropwise. After being stirred for ten minutes the mixture was acidified with glacial acetic acid, and the precipitated thyroxine was filtered off and redissolved in ethyl alcohol (20 ml.) and 2N-sodium hydroxide solution (10 ml.). The hot solution was acidified with acetic acid; the thyroxine separated as a microcrystalline powder (2·6 g.; 90%), m. p. 231—232° (decomp.).

3 : *5-Di-iodo-N-acetylthyroxine*. To a solution of **3** : 5-di-iodothyronine methyl ester (1 g.) in anisole (30 ml.), a solution of acetyl chloride (0·072 g.) in anisole (2 ml.) was added. Later the precipitate was filtered off and identified by m. p. and mixed m. p. [227° (decomp.)], as **3** : 5-di-iodothyronine methyl ester hydrochloride (0·84 g.). The filtrate was evaporated to dryness *in vacuo* and the residue was

dissolved in ethyl alcohol (5 ml.) and N-sodium hydroxide (5 ml.). After one hour N-hydrochloric acid (5 ml.) and water (20 ml.) were added to precipitate a white solid which was recrystallised from glacial acetic acid. It formed white prisms, m. p. 207—208° (0·35 g.) (Found: C, 36·0; H, 2·65; N, 2·2; I, 44·8. $C_{17}H_{11}O_3NI_4$ requires C, 36·0; H, 2·7; N, 2·5; I, 44·8%).

3·5-*Di-iodo-N-β-carboxypropionylthyronine*. To a solution of **3**:5-di-iodothyronine methyl ester (1 g.) in anisole (20 ml.) a solution of β-carbethoxypropionyl chloride (0·07 g.) in anisole (2 ml.) was added. The precipitated **3**:5-di-iodothyronine methyl ester hydrochloride was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in ethyl alcohol (5 ml.) and N-sodium hydroxide (5 ml.). After one hour N-hydrochloric acid (5 ml.) was added and the solid filtered off. It was dissolved in alcoholic alkali, treated with charcoal, and reprecipitated with acid to give tiny white prisms of **3**:5-*di-iodo-N-β-carboxypropionylthyronine* (0·3 g.), m. p. 231—232° (decomp.) (Found: N, 2·2; I, 41·2. $C_{19}H_{17}O_7NI_2$ requires N, 2·2; I, 40·7%).

Using the above method of iodination *N*-formyl-, *N*-acetyl-, and *N*-β-carboxypropionyl-thyroxine and 5-[**3**:5-di-iodo-4-(**3**:5-di-iodo-4-hydroxyphenoxy)benzyl]hydantoin were prepared from the corresponding derivatives of **3**:5-di-iodothyronine and 5-(3:5-di-iodo-4-*p*-hydroxyphenoxybenzyl)-hydantoin.

Thyroxine methyl ester. To a solution of **3**:5-di-iodothyronine methyl ester (1 g.) in N-butylamine (10 ml.) and methyl alcohol (20 ml.) a solution of iodine (1 g.) in methyl alcohol (10 ml.) was added. After one hour methanolic hydrogen chloride was added until the reaction solution was acid; dilution with water containing a little sodium acetate precipitated the crude ester which was extracted with methyl alcohol to give the pure compound (0·7 g.), m. p. and mixed m. p. 158°.

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RESEARCH DIVISION, GLAXO LABORATORIES, LTD.,
GREENFORD, MIDDLESEX.

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170. *Studies in Co-ordination Chemistry. Part I. Complexes of Quadrivalent Platinum with Tertiary Arsines.*

R. S. NYHOLM.

A series of octahedral complexes of quadrivalent platinum which have the general formula $Pt(Hal)_4.2AsR_3$ have been prepared by using various halides and tertiary arsines. They are all very stable compounds which are difficult to reduce. The complexes are more deeply coloured than their bivalent, planar analogues and are less soluble than these in organic solvents. Differences in reactivity between *cis*- and *trans*-isomers of these octahedral complexes similar to those shown by the bivalent square complexes have been observed. The properties of the compounds are discussed.

THIS paper is the first of a series dealing with the complexes of metal salts with tertiary arsines. It is proposed to investigate the properties of these complexes as a function of the valency state of the metal and of the anion present and to attempt the preparation of halogen-bridged complexes. Initially the investigation is confined to the elements of Group VIII. Tertiary arsines and phosphines show many properties as ligands which distinguish them from ammonia and amines; they have a very marked tendency to form non-ionic complexes which are freely soluble in organic solvents rather than salt-like substances which are formed so readily by ammonia. It is thus possible to apply a variety of techniques to the study of these compounds which cannot be used with ammines because of their insolubility in organic solvents. A detailed discussion of these differences and an attempt to explain them with particular reference to the nature of the metal–arsenic bond will be given in a later communication. However, the complexes of the elements in many of their valency states with tertiary arsines have not been investigated, and as a first step the preparation of these and a study of their properties were considered desirable.

Tertiary arsines have been used frequently for the stabilisation of lower-valency states, for which purposes their reducing properties are an advantage. In higher-valency states, however, any tendency towards dissociation of the complex might be expected to lead to decomposition, since the compound contains both an oxidising and a reducing agent combined. For instance, Mann and Purdie (*J.*, 1940, 1235) observed that several of the complexes of tervalent gold with triethylphosphine were unstable on standing; triethylphosphinetrichlorogold(III), $[AuCl_3.PEt_3]$, for example, decomposed within a few days on standing at room temperature, even when kept in the dark, metallic gold being deposited. The tri-iodide decomposed within a few weeks but the tribromide was stable indefinitely. Although tertiary phosphines are as a rule stronger ligands than tertiary arsines, they are similar to them in many ways; thus both tend to form non-ionic complexes with metal salts of the same general type and both are strong reducing agents.

No complexes of quadrivalent platinum with tertiary arsines have been described previously. Of similar complexes with tertiary phosphines, Cahours and Gal (*Compt. rend.*, 1870, **70**, 902) mentioned two platinic complexes with triethylphosphine but no analyses were given. Also, Rosenheim and Lowenstamm (*Z. anorg. Chem.*, 1903, **37**, 400) prepared the compound $PtCl_4.2P(OC_2H_5)_3$ but no analyses were reported.

All the platinic complexes described in this paper have the general formula $Pt(Hal)_4.2AsR_3$, and where solubilities permitted the determination of molecular weights in freezing benzene or freezing bromoform they were monomeric. All were prepared by adding the appropriate amount of the required halogen dissolved in carbon tetrachloride to the planar four-covalent complex of bivalent platinum dissolved in chloroform or benzene. The solvent used was very important in many cases, for the chloride complexes were often obtained as difficultly crystallisable oils from solvents other than benzene. Complexes of triethyl-, triphenyl-, and diphenylmethylarsine have been studied; the last has been found convenient for many other Group VIII metals but on occasions it led to the formation of isomeric mixtures. In all cases the platinic complexes were less soluble in organic solvents than the corresponding bivalent compounds from which they were derived. As with the bivalent complexes, solubility of the *cis*-bisarsine compounds was much less than that of the corresponding *trans*-isomers. For any given isomer the solubility decreased in the sequence chloride > bromide > iodide. As expected, the solubility of the bistriethylarsine complexes was much greater than that of the triphenyl or mixed aryl-alkyl derivatives.

The complexes were all highly coloured, the colour deepening in passing from the bivalent to the quadrivalent state and also in passing from the chloride through the bromide to the iodide. Where obtained, the *cis*-isomers were lighter in colour than the *trans*-isomers. The properties of a typical series are shown in the table

			Bivalent compounds.	
Platinic complex.	Colour.	M. p.	Colour.	M. p.
cis-$PtCl_4.2AsEt_3$	Pale yellow	125°	White	142°
trans-$PtCl_4.2AsEt_3$	Dark yellow	155	Yellow	120
trans-$PtBr_4.2AsEt_3$	Scarlet	173	Deep yellow	120
trans-$PtI_4.2AsEt_3$	Purplish-black	144	Orange	94

Probably the most noteworthy property of the complexes was their stability on standing and towards reducing agents. Only with the *cis*- and the *trans*-form of the *chloride* $PtCl_4.2AsEt_3$ was instability on standing observed; these two substances became oily after several months but the corresponding *tetrabromide* and *tetraiodide* were stable indefinitely Complexes of the other arsines showed no sign of decomposition after several months. On heating, the complexes melted without decomposition as a rule, in some cases above 200°. Unlike the triethylphosphine–gold complexes, they could be boiled with alcohol or acetone without reduction taking place. Sulphur dioxide similarly did not cause reduction except in one or two cases. Thus, although the *compounds* $PtCl_4.2AsMePh_2$ and $PtI_4.AsMePh_2$ were not reduced by sulphur dioxide in chloroform solution, the *complex trans*-$PtCl_2I_2.2AsMePh_2$ was reduced in ½ hour by this means; the product was *trans*-$PtI_2.2AsMePh_2$, the more electronegative halogen being removed. On the other hand, if one attempted to reduce the *cis*-dichloro-*trans*-di-iodo-compound, disproportionation to form the tetrachloro- and tetraiodo-compounds occurred without reduction taking place. Throughout the investigation it was observed that the mixed halogen compounds disproportionated very easily.

Towards most chemical reagents the *trans*-compounds were less reactive than the corresponding *cis*-isomers. For instance, an alcoholic solution of *cis*-$PtCl_4.2AsEt_3$ reacted instantly with aqueous silver nitrate but the corresponding *trans*-complex gave no precipitate for some hours. Similarly, the *cis*-compound reacted vigorously with concentrated sulphuric acid, an effervescence occurring with the evolution of hydrogen chloride; the *trans*-compound dissolved to an orange solution which slowly charred. This difference in reactivity is similar to that observed for the *cis*- and *trans*-planar complexes of bivalent platinum.

Some interesting facts on *cis–trans*-isomerism were noticed. Jensen (*Z. anorg. Chem.*, 1936, **229**, 225) observed that stability of *cis*-isomers of the type $Pt(Hal)_2.2AsEt_3$ increased in passing from the iodide to the chloride; the *cis*-di-iodo-complexes had to be made indirectly and soon reverted to the *trans*-forms on heating. This behaviour has also been observed with the diphenylmethylarsine anologues; the iodide forms a complex which is readily soluble in benzene and is undoubtedly the *trans*-form, but the much less soluble *cis*-form is favoured by the chloride and bromide. The equilibrium between *cis*- and *trans*-forms appeared to be much affected by both solvent and temperature in the cases of the chloride and bromide, which made the prepar-

ation of pure isomers difficult. The tetrabromo- and tetrachloro-platinum complexes of this arsine favoured the *cis*-form. An interesting difference was observed between the stabilities of the *cis*- and the *trans*-form of $PtCl_4.2AsEt_3$ and the corresponding tetrachlorides. The white *cis*-platinous complex required heating in solution for many days to convert it into the more soluble, yellow *trans*-isomer. However, the corresponding *cis*-tetrachloro-complex formed a considerable amount of the darker yellow *trans*-isomer on being left in the sunlight for a few hours. In these circumstances the *cis*-platinous complex was stable indefinitely. It appears to be well established that the stability of the *cis*-forms, both of bivalent and of quadrivalent platinum, increases with increasing electronegativity of the attached halogen, but steric factors depending on the particular arsine used are also important.

As expected for octahedrally co-ordinated quadrivalent complexes using d^2sp^3 bonds, the complexes are diamagnetic and the specific susceptibility of the compound $PtBr_4.2AsMePh_2$ ($\chi = -0{\cdot}41 \times 10^{-6}$) is of the order found by Asmussen (Doctorial Thesis, Copenhagen, 1941) for a large number of quadrivalent platinum complexes.

Apart from two complexes involving the $[PtCl_4]^{2-}$ ion, no salt-like complexes with tertiary arsines were isolated, and all attempts to obtain tertiary arsine complexes corresponding to ammines such as $[Pt(NH_3)_5Cl]Cl_3$ or $[Pt(NH_3)_4Cl_2]Cl_2$ were unsuccessful. Also, no halogen-bridged quadrivalent complexes were isolated. It is concluded from a study of these very stable complexes that combination of a tertiary arsine with a metal in a high oxidation state does not lead to instability provided that strong covalent bonds are formed between the metal and the arsenic atom.

Experimental.

Complexes of Triethylarsine.—Bivalent compounds. These were all prepared by Jensen's method (*Z. anorg. Chem.*, 1936, **229**, 225). The colour and m. p.s (Jensen's m. p.s in parentheses) were: *cis*-$PtCl_2.2AsEt_3$, white, m. p. 142° (142—142·5°); *trans*-$PtCl_2.2AsEt_3$, yellow, m. p. 119° (120—121°); *trans*-$PtBr_2.2AsEt_3$, deep yellow, m. p. 120° (120—121°); *trans*-$PtI_2.2AsEt_3$, orange, m. p. 92° (94°). The yield of *trans*-$PtCl_2.2AsEt_3$ was very much smaller than that of the *cis*-isomer produced simultaneously. The *cis*- was converted into the *trans*-form by refluxing in chloroform solution for several days, the isomerisation being very slow.

Jensen (*loc. cit.*) assigned the *cis*- and *trans*-configurations to the above compounds on the basis of their electric dipole moments in benzene, that of the *trans*-forms being zero and that of the *cis*- being in the vicinity of 10 Debye units. He pointed out that the *trans*-isomers differed from the *cis*- in several of their physical properties, and foremost amongst these were their colours and solubilities in benzene. The *trans*-forms were deeper in colour and were much more soluble in benzene than the *cis*-isomers. Special consideration has been given to these properties in the assignment of the *cis*- or *trans*-configuration to the various platinous complexes described here.

Bistriethylarsinetetrachloroplatinum(IV). (i) *trans*-Isomer. *trans*-Bistriethylarsinedichloroplatinum(II) (1·1 g.), dissolved in cold chloroform (25 ml.), was treated with gaseous chlorine until no further absorption occurred. The solution became warm and changed colour from deep yellow to orange red. The chloroform was then removed at the pump at room temperature, and the orange residue recrystallised from alcohol. The *compound* was obtained as short, stumpy, dark yellow crystals, m. p. 155° (Found: C, 21·7; H, 4·6; Pt, 19·5; *M*, cryoscopic in 2·58% solution in benzene, 630. $C_{12}H_{30}Cl_4As_2Pt$ requires C, 21·75; H, 4·5; Pt, 19·5%; *M*, 661). It dissolved readily in benzene and other organic solvents except light petroleum. An acetone solution gave no reaction with silver nitrate unless heated and left for some time. After many months' standing the compound became oily.

(ii) *cis*-Isomer. *cis*-Bistriethylarsinedichloroplatinum(II) (1·2 g.), dissolved in chloroform (15 ml.), was treated with gaseous chlorine as above, the solution becoming warm and acquiring a bright yellow colour. After removal of the chloroform at room temperature at the pump, the yellow residue was recrystallised from alcohol. The *compound* was obtained as yellow needles which formed a characteristic mat; it was much lighter in colour than the *trans*-isomer and melted at 125° (Found: C, 21·9; H, 4·7; Pt, 19·5%). It was moderately soluble in alcohol and acetone but practically insoluble in benzene even when boiling. If heated under reflux for a long time with benzene it gradually dissolved to a yellow solution of the *trans*-isomer. This change also occurred on standing in sunlight, a behaviour in marked contrast with that of the bivalent *cis*-compound which on standing shows no tendency at all to change into the *trans*-isomer. An acetone solution gives an immediate copious precipitate with silver nitrate solution, a reaction in which it differs from the *trans*-isomer. When treated with concentrated sulphuric acid, the *cis*-isomer reacted immediately with effervescence with the evolution of hydrogen chloride; when similarly treated, the *trans*-isomer dissolved to an orange solution and slow charring then took place.

trans-*Bistriethylarsinetetrabromoplatinum*(IV). *trans*-Bistriethylarsinedibromoplatinum(II) (1·40 g.), dissolved in benzene (15 ml.) (yellow solution), was treated with bromine (0·34 g.) in carbon tetrachloride (4 ml.) and the solution immediately became deep red. Evaporation at the pump at ordinary temperatures yielded beautiful scarlet crystals m. p. 172° raised by recrystallisation from alcohol to 173°. The *compound* crystallised as flat rhombs (Found: Pt, 23·2; *M*, cryoscopic in 1·33% solution in benzene, 775. $C_{12}H_{30}Br_4As_2Pt$ requires Pt, 23·3%; *M*, 839). It dissolved readily in organic solvents, particularly benzene and chloroform. An acetone solution slowly precipitated silver chloride on treatment with silver nitrate.

trans-*Bistriethylarsinetetraiodoplatinum*(IV).—*trans*-Bistriethylarsinedi-iodoplatinum(II) (1·2 g.), dis-

solved in chloroform (30 ml.), was treated with iodine (0·4 g.) dissolved in chloroform (40 ml.), the light orange solution turning to a dark wine-red colour. After evaporation of the chloroform at the pump, the residue was recrystallised from alcohol. The *compound* was obtained as purplish black, flat rectangular crystals, m. p. 144° (Found: Pt, 18·9. $C_{18}H_{30}I_4As_2Pt$ requires Pt, 19·0%); it was readily soluble in benzene and chloroform to a red solution but less soluble than either the chloride or the bromide.

Complexes of Triphenylarsine.—*cis*-Bistriphenylarsinedichloroplatinum (II) was prepared according to Jensen (*loc. cit.*). It decomposed above 300° on heating (Found: Pt, 22·0. Calc. for $C_{36}H_{30}Cl_2As_2Pt$: Pt, 22·0%).

trans-Bistriphenylarsinedichloroplatinum(II) was prepared from the *cis*-isomer by Jensen's method (*loc. cit.*). He recommended refluxing in chloroform for 15 minutes, but in this experiment the *cis*-isomer (0·65 g.) was refluxed with chloroform (36 ml.) for 1¼ hours, the almost colourless solution turning deep yellow. Removal of the chloroform gave a compound slightly more yellow than the starting material. This was dissolved in benzene (50 ml.) by refluxing, cooled, and treated with chlorine (0·05 g.) in carbon tetrachloride (2 ml.). The solution became bright yellow and on concentration it afforded yellow crystals which can be recrystallised from benzene with difficulty in small quantities; m. p. 290° (Found: Pt, 20·7. $C_{36}H_{30}Cl_2As_2Pt$ requires Pt, 20·6%). Owing to the low solubility of complexes of this *tetrachloroarsine*, no other complexes were prepared.

Complexes of Diphenylmethylarsine.—*Bisdiphenylmethylarsinedichloroplatinum*(II). This compound was isolated in two forms; one is an almost white, crystalline substance, m. p. 223°, practically insoluble in organic solvents, and the other is light yellow and slightly more soluble, and on heating softens first at 207° and then melts at 214°. On standing or heating, the form of m. p. 214° changes over into that of m. p. 223°, which is no doubt the *cis*-isomer. Unfortunately, low solubility in cold benzene prevented confirmation of this by electric-dipole measurements. Burrows and Parker (*J. Proc. Roy. Soc. N.S.W.*, 1934, **68**, 39) obtained these compounds, one as yellow prisms, m. p. 207° readily soluble in toluene, and the other as yellow needles, m. p. 218°, much less soluble in toluene.

Low-melting form. Diphenylmethylarsine (1·5 g.), dissolved in alcohol (50 ml.), was added to hexahydrated chloroplatinic acid (1·0 g.) dissolved in alcohol (150 ml.), and the solution heated on the water-bath for one hour. Yellow crystals began to form, and on cooling an almost quantitative yield (1·4 g.) was obtained (Found: C, 41·3; H, 3·4; Cl, 9·3; Pt, 25·9. Calc. for $C_{26}H_{32}Cl_2As_2Pt$: C, 41·3; H, 3·4; Cl, 9·4; Pt, 25·8%). The compound was washed many times with alcohol, recrystallisation being difficult without change into the other form taking place. It was readily soluble in chloroform, fairly soluble in acetone but less soluble in cold benzene, from which it crystallised as the other form.

High-melting form. This preparation is commenced as for the other isomer but more concentrated solutions are used. Diphenylmethylarsine (7 g.), dissolved in alcohol (250 ml.), was added to hexahydrated hexachloroplatinic acid (5 g.) dissolved in alcohol (250 ml.). After a few seconds' heating an orange-yellow precipitate appeared which decomposed on further heating, forming a yellow, horny mass and a white powder. The mixture was heated for about an hour, the mass being occasionally broken up, and was then filtered and the residue extracted with chloroform. Removal of chloroform from the almost colourless solution gave a white compound, m. p. 223°, which was less soluble than the other isomer in all solvents (Found: C, 41·4; H, 3·5; Pt, 25·8%).

Two by-products were isolated during a study of the above reaction. When the arsine and chloroplatinic acid reacted in cold alcoholic solution, a yellow precipitate was obtained after about 20 seconds. This substance was insoluble in all solvents, and heating caused decomposition in all solvents tried. The composition varied slightly (C, 30·2—30·8; H, 3·0—3·4; Cl, 13·6; Pt, 23·9—24·7%), but agreed fairly well with $[Pt(AsMePh_2)_4][PtCl_4]$ which requires C, 39·5; H, 3·29; Cl, 13·65; Pt, 24·75%. Its insolubility supports the above formulation and it may be similar to salts of the type $[Pt(AsR_3)_4][PtCl_4]$ isolated by Jensen using trialkylarsines. It is suggested that the platinichloride, rather than the platinochloride, was formed here because reduction with diphenylmethylarsine proceeds more slowly than with trialkylarsines and the temporary co-existence of $[Pt(AsR_3)_4]^{2+}$ and $[PtCl_4]^{2-}$ ions is feasible. From the filtrate of this preparation large orange crystals were obtained after standing for 24 hours. These had m. p. 224° (decomp.) and were insoluble in all solvents. The compound was decomposed by heating with dilute sodium hydroxide solution. The analysis (Found: C, 34·4; H, 3·1; Cl, 23·8; Pt, 21·2%) suggests a formulation as the *salt* $[HAsMePh_2]_2[PtCl_4]$, which requires C, 34·7; H, 3·12; Cl, 23·7; Pt, 21·7%. This substance appears to be one of the few cases where addition of a proton to a tertiary arsine takes place.

Bisdiphenylmethylarsinedibromoplatinum(II).—Diphenylmethylarsine (1·5 g.), dissolved in alcohol (125 ml.), was added to a solution of sodium bromide (5 g.) in distilled water (25 ml.), and the solution added to hexahydrated chloroplatinic acid (1·0 g.) dissolved in alcohol (25 ml.). The buff-coloured precipitate first formed gradually dissolved on heating on the water-bath and the solution lightened in colour. The bright yellow crystals which were slowly precipitated were filtered off after about 2 hours and well washed with alcohol. After recrystallisation from acetone the compound melted at 201° (Found: C, 37·5; H, 3·1; Pt, 23·1. Calc. for $C_{26}H_{32}Br_2As_2Pt$: C, 37·0; H, 3·1; Pt, 23·1%). Burrows and Parker (*loc. cit.*) first described this compound and reported m. p. 196°. It is only very slightly soluble in cold benzene but dissolves on heating; the low solubility in benzene in comparison with that of the iodide indicates that the compound is almost certainly the *cis*-form.

Bisdiphenylmethylarsinediiodoplatinum(II).—Diphenylmethylarsine (1·5 g.) and potassium iodide (5 g.), dissolved in a mixture of water (30 ml.) and alcohol (150 ml.), were added to hexahydrated hexachloroplatinic acid (1·0 g.) dissolved in alcohol (20 ml.). The pale pink precipitate which formed at once gradually darkened on heating on the water-bath and after about 3 hours was replaced by a pinkish-orange crystalline powder in a colourless solution. This precipitate was then filtered off, washed many times with alcohol, and recrystallised from benzene and light petroleum; m. p. 229° (Found: C, 33·3; H, 2·8; Pt, 20·6. $C_{26}H_{32}I_2As_2Pt$ requires C, 33·3; H, 2·8; Pt, 20·8%). The *compound* dissolved very readily in chloroform and cold benzene and was fairly soluble in acetone. From its ready solubility in benzene it is undoubtedly the *trans*-isomer.

Bisdiphenylmethylarsinetetrachloroplatinum(IV). This *compound* had to be prepared in benzene

solution for it was obtained from chloroform–carbon tetrachloride as a low-melting, difficultly crystallisable substance containing solvent which was very difficult to remove. Bisdiphenylmethylarsinedichloroplatinum (II) (m. p. 223°) (0·75 g.) was dissolved in benzene (75 ml.) by heating under reflux, and chlorine (0·075 g.) in carbon tetrachloride (10 ml.) was added to the warm solution. The light yellow solution deepened in colour and after removal of about half of the solvent the compound crystallised as deep yellow microcrystalline rods (0·6 g.) which were filtered off and washed with benzene, in which they are only very slightly soluble. It may be recrystallised from benzene, the m. p. varying from 205° to 215°, the lower m. p. form gradually increasing on standing (Found, for form of m. p. 205°: C, 37·4; H, 3·1; Pt, 23·9. Found, for form of m. p. 215°: C, 37·8; H, 3·1; Cl, 17·3; Pt, 23·7. $C_{26}H_{26}Cl_4As_2Pt$ requires C, 37·6; H, 3·1; Cl, 17·4; Pt, 23·7%). The substance appears to be an equilibrium mixture of *cis*- and *trans*-forms, but attempts to separate them were not successful. Owing to the low solubility even in bromoform the molecular weight could not be determined.

Bisdiphenylmethylarsinetetrabromoplatinum(IV). Bisdiphenylmethylarsinedibromoplatinum(II) (m. p. 201°) (3·05 g.), dissolved in chloroform (35 ml.), was treated with bromine (0·58 g.) dissolved in carbon tetrachloride (9 ml.) at room temperature. The yellow solution immediately became orange-red in colour and was concentrated at room temperature at the pump to about 10 ml. Orange crystals of the *tetrabromo*-compound (3·1 g.) crystallised out, and were recrystallised from chloroform–carbon tetrachloride. The m. p. varied from 212° to 218°, but after standing for some weeks the compound melted at 214° (Found: C, 31·5; H, 2·7; Pt, 19·3%). The first preparation melted at 227° (Found: C, 30·6; H, 2·9; Br, 31·9; Pt, 19·1%; *M*, cryoscopic in 0·737% solution in bromoform, 907. $C_{26}H_{26}Br_4As_2Pt$ requires C, 31·1; H, 2·6; Br, 31·9; Pt, 19·4%; *M*, 1003) and was more soluble in organic solvents, but heating, recrystallisation, or standing caused a gradual fall in the m. p. to that of the less soluble form. The compound (m. p. 214°) is soluble in chloroform, slightly soluble in benzene, but practically insoluble in alcohol or acetone, and is quite insoluble in ether or light petroleum; it is too insoluble both in freezing bromoform and in boiling benzene for the molecular weight to be determined.

The form of m. p. 227° is probably *trans*-, and the other an equilibrium mixture of *cis*- and *trans*-isomers.

Bisdiphenylmethylarsinetetraiodoplatinum(IV). Bisdiphenylmethylarsinedi-iodoplatinum(II) (*trans*) (1·76 g.), dissolved in chloroform (25 ml.), was treated with iodine (0·45 g.) dissolved in chloroform–carbon tetrachloride (10 ml.; 1 : 1). After a few seconds the light orange solution became dark wine-red in colour and glistening purplish-black crystals were precipitated. The solution was concentrated to about 15 ml. at room temperatures at the pump, and a yield of 1·9 g. of the *tetraiodide* was obtained which melted at 193° after recrystallisation from chloroform and carbon tetrachloride. The compound is fairly soluble in chloroform and bromoform but not very soluble in benzene. Its properties indicate that it is the *trans*-isomer (Found: C, 25·8; H, 2·4; I, 42·6; Pt, 16·2%; *M*, cryoscopic in 0·507% solution in bromoform, 1100. $C_{26}H_{26}I_4As_2Pt$ requires C, 26·2; H, 2·2; I, 42·6; Pt, 16·4%; *M*, 1191).

Bisdiphenylmethylarsinedichlorodibromoplatinum(IV). Oxidation of *cis*-$PtCl_2$·2AsMePh_2 with bromine or of *cis*-$PtBr_2$·2AsMePh_2 with chlorine gave the same product (m. p. and mixed m. p.): it may be an equilibrium mixture.

The dibromo-compound (m. p. 201°) (0·84 g.) in chloroform (25 ml.) was treated with chlorine (0·071 g.) in carbon tetrachloride (5 ml.) and the yellow solution turned orange. Carbon tetrachloride (10 ml.) was added, and the solution concentrated to half bulk, filtered from a small amount of sticky material, and then evaporated to dryness, and the residue was recrystallised from carbon tetrachloride–chloroform. The *compound* was obtained as a microcrystalline powder, m. p. 203° (Found: C, 34·3; H, 2·9; Pt, 21·1. $C_{26}H_{26}Cl_2Br_2As_2Pt$ requires C, 34·1; H, 2·8; Pt, 21·3%). It was also prepared by the action of bromine (0·09 g.) in carbon tetrachloride (1·5 ml.) on the chloro-compound (m. p. 223°) (0·4 g.) dissolved in benzene (60 ml.) by heating. After evaporation of the bulk of the solvent, the orange complex was obtained; m. p. 203°. Solubilities are low, suggesting that the two arsine groups are *cis*-, but the configuration of the halogens is unknown.

Bisdiphenylmethylarsinedichlorodi-iodoplatinum(IV). This compound was prepared by two methods. (*a*) Bisdiphenylmethylarsinedi-iodoplatinum(II) (m. p. 229°, *trans*-) (1·9 g.) was dissolved in chloroform (30 ml.), and chlorine (0·142 g.) in carbon tetrachloride (10 ml.) added. The solution was kept cold and changed colour from pink to dark wine-red. Concentration at the pump at room temperature precipitated a brownish powder, m. p. 163°. The compound crystallised as brown rods; it was not recrystallised for fear of disproportionation.

(*b*) Bisdiphenylmethylarsinedichloroplatinum(II) (m. p. 214°) (0·75 g.) was dissolved in cold chloroform (30 ml.), and iodine (0·25 g.) in carbon tetrachloride–chloroform (10 ml.; 1 : 1) added. The very pale yellow turned to a dark red colour, and evaporation at room temperature at the pump to a volume of 10 ml. precipitated light brown crystals of the required complex, m. p. 163° (Found: C, 31·2; H, 2·6; Pt, 19·3. $C_{26}H_{26}Cl_2I_2As_2Pt$ requires C, 30·9; H, 2·6; Pt, 19·3%).

From its method of preparation this compound is clearly a trans-*dichloro*-trans-*di-iodobisarsine* complex. Attempts to obtain an analytically pure specimen of the *cis*-dichloro-*trans*-di-iodo-complex were unsuccessful because disproportionation occurred so rapidly that the first fraction crystallising from the reaction mixture was contaminated with the tetraiodo-compound.

Reduction of Bisdiphenylmethylarsinedichlorodi-iodoplatinum(IV). The above *trans*-compound (0·5 g.), freshly prepared by the action of chlorine on the *trans*-di-iodo-compound, was dissolved in cold chloroform (25 ml.), and sulphur dioxide bubbled through the dark red solution. The colour faded during the first 15 minutes and after about an hour had become light orange, and was then apparently unaltered. The solution was filtered, the chloroform removed at the pump, and the pinkish-brown residue recrystallised twice from benzene and light petroleum, pink needles being obtained, m. p. (and mixed m. p. with a pure specimen of *trans*-di-iodo-compound) 229°. Attempts to reduce the tetrahalogeno-compound by boiling with acetone, the method used by Mann and Purdie (*loc. cit.*) for the auric complexes, were not successful.

Bisdiphenylmethylarsinedibromodi-iodoplatinum(IV). Bisdiphenylmethylarsinedibromoplatinum(II) (m. p. 201°) (0·84 g.), dissolved in chloroform (30 ml.), was treated with iodine (0·25 g.) dissolved in

carbon tetrachloride–chloroform (30 ml.; 1 : 1) and the yellow orange solution immediately turned dark red. Removal of most of the solvent at room temperatures at the pump gave glistening black crystals which disproportionated when attempts were made to carry out recrystallisation. The *compound* melts at 185°, and from the analysis (Found: C, 27·6; H, 2·5; Pt, 17·5. $C_{36}H_{33}Br_2I_2As_3Pt$ requires C, 28·3; H, 2·4; Pt, 17·8%) appears to contain traces of the tetraiodide. In view of their instability these complexes were not further investigated.

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON. [*Received, November 7th*, 1949.]

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171. *Studies in Co-ordination Chemistry. Part II. Trisarsine Complexes of Bivalent Platinum and Palladium.*

By R. S. NYHOLM.

The compounds $PtBr_2.3AsR_3$ and $PdBr_2.3AsR_3$ (where AsR_3 is diphenylmethylarsine) have been isolated and their properties investigated. Although their solubility in organic solvents suggested that they were non-ionic covalent complexes, it was found that they dissolved in these solvents with dissociation. Electrical-conductivity measurements in acetone solution on the palladium compound support the view that they are salts of the triammine type, *i.e.*, $[Pd(AsR_3)_3Br]^+Br^-$.

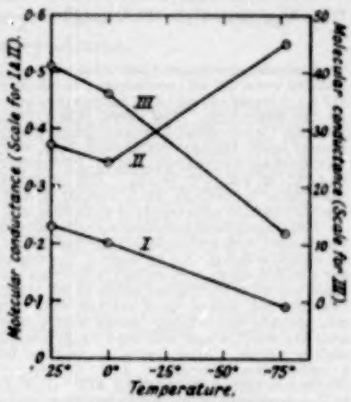
DURING an investigation of the tertiary arsine complexes of metal salts, two new complexes of bivalent platinum and palladium have been isolated of a type not previously described, and their properties were carefully investigated because their behaviour at first suggested that they might be examples of five-covalency similar to that observed by Jensen and Nygaard (*Acta Chem. Scand.*, 1949, **3**, 474) in the nickel compound $NiBr_2.2PEt_3$. When preparing the compound $PtBr_2.2AsMePh_2$ by the action of diphenylmethylarsine on chloroplatinic acid in the presence of excess of sodium bromide, it was observed that excess of the arsine led to the formation of an orange crystalline *compound* of empirical formula $PtBr_2.3AsMePh_2$. Further investigation showed that this orange compound could be obtained readily by heating the bisarsine compound ($PtBr_2.2AsMePh_2$) with excess of arsine in alcohol solution under reflux, the trisarsine compound crystallising out on cooling. This complex dissolved readily in chloroform or benzene on shaking and was fairly soluble in acetone and warm alcohol. From the alcoholic solution the bisarsine compound was precipitated on cooling unless excess of arsine was present. The trisarsine compound melted at 151° as compared with 201° for the yellow bisarsine complex.

The corresponding *palladium* compound was prepared in a similar manner, starting with the orange *compound* $PdBr_2.2AsMePh_2$ and using a greater excess of arsine. Conditions were found to be more critical than in the case of the platinum compound, for the trisarsine complex dissociated very readily. It forms almost black crystals which melt at 109°, the colour changing to light orange; the bisarsine complex melts at 178°. The trisarsine compound dissolved very readily in organic solvents such as acetone, benzene, and chloroform, and was fairly soluble in alcohol, the black crystals giving an orange solution.

The molecular weights of both of these compounds were measured in a variety of solvents, benzene, bromoform, ethylene dibromide, and acetone being used; in the first three the determinations were cryoscopic, in the last ebullioscopic. In every case a molecular weight corresponding to half of the formula weight $MBr_2.3AsMePh_2$ (M = Pd or Pt) was observed because the compounds dissociated into one molecule each of arsine and the bisarsine compound; from benzene solution the bisarsine complexes were precipitated at the freezing point.

There are four obvious ways in which these compounds might be formulated: (*a*) as a molecular (lattice) compound of arsine and the bisarsine complex; (*b*) as a bridged complex of two octahedrally co-ordinated bivalent metal atoms, requiring a molecular formula $(MBr_2.3AsMePh_2)_2$; (*c*) as a salt of the type $[M(AsR_3)_3Br]^+Br^-$; (*d*) as a five-covalent complex in which the extra molecule of arsine forms a very weak bond to the metal atom by using the remaining 5*p* or 6*p* orbital. Since a solution of the compound shows some properties different from those expected of a mixture of its constituents, (*a*) is excluded; (*b*) is readily disposed of since neither molecular weight nor solubility lends any support, and in any case six-covalent complexes of bivalent palladium and platinum are very rare. Solubility in organic solvents and low melting point and the fact that such a complex should dissociate readily lent some support to (*d*), but the salt-like structure (*c*) has been finally accepted from studies on the conductivity of the palladium complex in acetone. The higher solubility of the palladium compound, particularly at low temperatures, made it preferable to the platinum complex for this purpose.

A solution of the palladium trisarsine complex in acetone has a very light orange colour at 25°, and is only very slightly darker than a solution of the bisarsine compound at the same concentration (M/100). When a solution of the bisarsine complex is cooled there is no perceptible change in colour but the trisarsine solution gradually deepens in colour as the temperature is reduced below −25°, and at about −78° the colour is deep red. As the trisarsine complex in the solid state is black with a red streak, it is reasonable to assume that recombination of the bisarsine complex and arsine to form the complex isolated in the solid state has taken place. This colour change is also observed if one cools similarly a mixture of free arsine and the bisarsine compound or a benzene solution of these two substances; the dark reddish-black mixture which is observed at low temperatures becomes orange again on warming to room temperatures. The great ease with which temperature caused dissociation, together with other properties mentioned above, led to the possibility of a weak covalent bond between the arsine and the metal. Conductivity measurements, however, show that at low temperatures an electrolyte is being formed. In the figure are shown the molecular conductivities of M/100-solutions of the bisarsine and the trisarsine complex in acetone at various temperatures, M/100-lithium bromide having been measured for comparison. Although for both lithium bromide and the bisarsine complex there is the expected decrease in conductivity as the temperature falls over the 100° range, yet the trisarsine complex shows a remarkable rise in conductivity below 0°. This increase in conductivity parallels the deepening in colour which occurs at the same temperature. No significance is attached to the actual conductance of $PdBr_2.2AsMePh_2$, and $PdBr_2.3AsMePh_2$ at 25°, it being due, no doubt, to traces of impurity or partial solvolysis; at −78°, however, it is clear that the amount of salt formation is more than sufficient to balance the natural decrease due to the fall in temperature. The amount of salt formation at −78° is still relatively small as judged by comparison with lithium bromide at the same temperature. One may conveniently represent the changes which take place when the trisarsine compound dissolves as follows:



I. M/100-$PdBr_2.2AsMePh_2$.
II. M/100-$PdBr_2.3AsMePh_2$.
III. M/100-LiBr.
(*All in acetone.*)

$$[Pd(AsR_3)_2Br]^+[Br]^- \xrightarrow{\text{Acetone}} PdBr_2.2AsR_3 + AsR_3 \underset{\text{Higher temperatures}}{\overset{\text{Low temperatures}}{\rightleftharpoons}} [Pd(AsR_3)_2Br]^+ + Br^-$$

Reddish-black crystals. — Light orange solution (room temperatures). — Dark red solution (−78°).

One originally confusing observation was the fact that it was found possible to dissolve in benzene a higher molar concentration of the platinum trisarsine complex than of the bisarsine complex alone; this appeared especially unusual since all measurements showed that the trisarsine complex immediately dissociated into the bisarsine complex and arsine. However, the presence of arsine may enhance the solubility to some extent, but of greater importance is the probable formation of the *trans*-bisarsine complex initially on dissociation. This is much more soluble than the *cis*-form but the latter is gradually produced on standing. The yellow bisarsine compound used in the preparation is only slightly soluble in benzene at room temperatures and is hence undoubtedly the *cis*-isomer.

These compounds appear to be the first known examples of salts of the triammine type formed by tertiary arsines or phosphines with bivalent platinum or palladium. These ligands, unlike ammonia, have a great tendency to form non-ionic complexes but some salt-like compounds have been obtained; Jensen (*Z. anorg. Chem.*, 1936, **229**, 225) described salts of the type $[Pt(PR_3)_4]Cl_2$ and $[Pt(PR_3)_4][PtCl_4]$ which passed over into the monomeric covalent complexes $PtCl_2.2PR_3$ on heating in organic solvents but no evidence of a trisarsine or trisphosphine complex was obtained. Morgan and Yearsley (*J.*, 1925, **127**, 184) have described complexes of

trialkylstibines similar to those isolated by Jensen. It is noteworthy that the iodide and bromide corresponding to the compounds described in this paper could not be obtained, and attempts to use trialkylarsines were unsuccessful; triphenylarsine also gave no trisarsine complex. Phenyldimethylarsine may be used instead of diphenylmethylarsine but the complexes are unsuitable for study because the arsine is very readily oxidised in air. The isolation of the compounds described in this paper must be ascribed to peculiarly favourable conditions of solubility not found with the other arsines or anions.

Like all bivalent complexes of palladium and platinum which have been measured, these trisarsine compounds are diamagnetic.

Experimental.

Bisdiphenylmethylarsinedibromopalladium(II).—Anhydrous palladous chloride (0·66 g.), dissolved in distilled water (33 ml.) containing a few drops of 10*N*-hydrochloric acid, was treated with sodium bromide (10 g.) in water (30 ml.) and diphenylmethylarsine (1·45 g.) in alcohol (150 ml.), and the solution heated on the water-bath. The initial yellow precipitate slowly redissolved on heating to form a reddish solution. After about ½ hour an orange precipitate gradually formed which was filtered off (2·1 g.) after several hours' heating on the water-bath, washed with cold aqueous alcohol and finally with water, and recrystallised from alcohol; m. p. 178° (Found: C, 41·2; H, 3·4; Pd, 14·0. $C_{26}H_{26}Br_2As_2Pd$ requires C, 41·3; H, 3·4; Pd, 14·1%). The *compound* crystallises as sparkling orange plates, readily soluble in chloroform or benzene, fairly soluble in acetone, but only slightly soluble in cold alcohol. Like all similar bisarsine compounds of palladium it is undoubtedly the *trans*-isomer.

Trisdiphenylmethylarsinemonobromopalladium(II) *Monobromide*.—The foregoing compound (0·34 g.) was treated with diphenylmethylarsine (3·0 g.) in alcohol (40 ml.) and heated to boiling. All dissolved to an orange solution, but on cooling, the original bisarsine complex crystallised out. (It is necessary to get concentrations just correct, otherwise the trisarsine complex is not obtained.) The solution was again heated to boiling and about 30 ml. of alcohol were removed by boiling, and on cooling slowly, dark brownish-red, almost black crystals were obtained. Formation of these crystals was hastened if the cold solution was carefully seeded with a crystal of the pure compound. The complex was filtered off after the solution had been kept for 24 hours and washed several times with cold alcohol, in which it is slightly soluble. After drying in a vacuum desiccator the *compound* was obtained as black crystals with a reddish streak [Found: C, 47·2; H, 3·95; Pd, 11·0%; *M* (cryoscopic), in bromoform (0·494%), 452; in ethylene dibromide (0·833%), 477. $C_{39}H_{39}Br_2As_3Pd$ requires C, 47·4; H, 4·0; Pd, 10·9%; *M*, 1003]. It dissolved readily in most organic solvents except light petroleum and was quite insoluble in water. On heating the compound melts at 109°, the colour changing instantly from black to orange.

Bisdiphenylmethylarsinedibromoplatinum(II).—This compound, m. p. 201°, prepared as in Part I (preceding paper), was recrystallised twice before use from acetone (Found: C, 37·5; H, 3·1; Pt, 23·1. Calc. for $C_{26}H_{26}Br_2As_2Pt$: C, 37·0; H, 3·1; Pt, 23·1%).

Trisdiphenylmethylarsinemonobromoplatinum(II) *Monobromide*.—The foregoing compound (4·0 g.) was heated under reflux with diphenylmethylarsine (5 g.) dissolved in alcohol (200 ml.) for about 15 minutes. Practically all the bisarsine complex had then dissolved, the solution becoming orange. The solution was filtered hot, and on cooling, orange crystals of the *trisarsine* compound were deposited. These were filtered off and washed many times with alcohol; yield, 4·07 g. [Found: C, 43·0; H, 3·5; Br, 14·8; Pt, 17·9%; *M*, in bromoform (cryoscopic), 0·875% soltn., 567, 1·45% soltn., 587; in ethylene dibromide (cryoscopic), 1·21% soln., 548; in acetone (ebullioscopic), 1·81% soln., 541; 3·70% soln., 560; in benzene * (cryoscopic), 1·60% soln., 485; 1·84% soln. 478. $C_{39}H_{39}Br_2As_3Pt$ requires C, 43·0; H, 3·6; Br, 14·7; Pt, 17·9%; *M*, 1087]. The compound melts sharply at 151° if heated fairly rapidly, the colour changing on fusion from orange to yellow. When cooled, the orange colour returns but the m. p. is then 2—3° lower, indicating that dissociation products are present. The compound is quite insoluble in water, practically insoluble in cold alcohol, but moderately soluble in acetone. An acetone solution slowly deposits yellow crystals of the bisarsine compound unless excess of arsine is added. On shaking, the compound dissolves fairly readily in benzene, chloroform, bromoform, and ethylene dibromide, but it is quite insoluble in light petroleum. Although an acetone solution reacts immediately with silver nitrate solution, this is not taken as significant, for the bisarsine complex also reacts immediately with silver nitrate.

Magnetic susceptibility. This was measured in powder form and the compound was found to be diamagnetic with a specific susceptibility $\chi_{293°K.} = -0{\cdot}46 \times 10^{-6}$.

Electrical conductivity. These measurements were carried out in a pipette-type cell of volume about 15 ml. The cell constant (0·0508 cm.$^{-1}$) was determined at 25° with N/100-potassium chloride. It was not re-determined at lower temperatures because only comparative values of conductivity were required. The acetone used was A.R., which was distilled over potassium permanganate, dried $[Mg(ClO_4)_2]$, and fractionated. The specific conductivity (κ) was $2{\cdot}1 \times 10^{-9}$, $1{\cdot}75 \times 10^{-9}$, and $7{\cdot}3 \times 10^{-9}$ mho/cm.[3] at 25°, 0°, and −78°, respectively. The $PdBr_2,2AsMePh_2$ and $PdBr_2,3AsMePh_2$ were recrystallised twice before use and dried in a vacuum desiccator. The N/100-solutions were made up at 25°. After measurement of the conductivity of a solution at 25°, the cell was placed in a bath of distilled water and ice, and the conductivity measured at 0°. The cell was then placed in a long Dewar flask containing alcohol and solid carbon dioxide, the flask being stoppered to prevent the entry of moisture. Throughout all measurements the temperature was checked with a toluene thermometer which remained constant to within 1° of −78°.

* The results in benzene are unreliable because the bisarsine compound crystallised out after about two determinations of the freezing point; the solution is supersaturated and this probably explains the larger depression.

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SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, November 7th*, 1949.]

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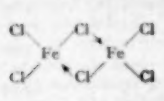
172. *Studies in Co-ordination Chemistry. Part III. Complexes of Iron with a Ditertiary Arsine.*

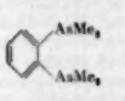
By R. S. NYHOLM.

Complexes of ferric and ferrous halides with the chelating group *o*-phenylenebisdimethylarsine have been prepared and studied. Ferric chloride and bromide give rise to highly coloured salt-like compounds in which the univalent cation contains two halogen atoms and two molecules of the chelate group bound to the iron atom. The anion may be a halide ion or the ions $[FeCl_4]^-$ or $[FeBr_4]^-$. The tetrabromoferrate ion is converted readily into the bromide ion by treatment with water in acetone solution. Magnetic measurements have established that the cation has an effective magnetic moment which corresponds to one unpaired electron and it is concluded that the bonds to the iron are covalent, forming an octaheral complex; in the anions $[FeCl_4]^-$ and $[FeBr_4]^-$ a magnetic moment corresponding to five unpaired electrons is observed and in these ions the binding is thus ionic. The perchlorates have been prepared, and studies of their magnetic susceptibility support the above conclusions. When treated with iodides, the chloride complex is reduced to a diamagnetic ferrous compound which is formulated as a non-ionic octahedral complex with covalent bonds. The corresponding diamagnetic ferrous bromide and ferrous thiocyanate complexes have been prepared and studied. The implications of the magnetic measurements are discussed. Attempts to isolate halogen-bridged octahedral complexes were unsuccessful.

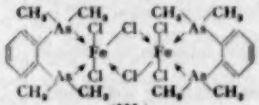
THE complexes of iron halides with a ditertiary arsine have been studied as part of an investigation of Group VIII elements in various valency states with tertiary arsines. The chelating group *o*-phenylenebisdimethylarsine was chosen for this investigation for two reasons. Earlier investigations using diphenylmethylarsine had yielded complexes of ferric chloride which dissociated so readily in solution that it was possible only to speculate as to their structure (Nyholm, *J. Proc. Roy. Soc. N.S.W.*, **1944**, **78**, 229) and a much more powerful ligand was needed. Jensen (*Z. anorg. Chem.*, **1936**, **229**, 282) has reported that triethylphosphine, a stronger ligand than triethylarsine as a rule, does not co-ordinate with ferrous iron, and for this investigation the chelating group used was chosen because Chatt and Mann (*J.*, **1939**, 1622) had shown that it forms very strong bonds, at least with bivalent palladium; it was also chosen in an attempt to isolate halogen-bridged complexes of ferric iron.



(I.)



(II.)



(II*.)

Ferric chloride in the solid state has a layer structure with the ferric atom surrounded octahedrally by six chlorine atoms (Wooster, *Z. Krist.*, **1932**, **83**, 35) but it sublimes readily at 285°, and below 440° its vapour pressure corresponds to the formula Fe_2Cl_6. In organic solvents like ether, alcohol, acetone, and pyridine, ferric chloride is monomeric but there is evidence for dimerisation in solvents like carbon disulphide, chloroform, and benzene (Wells, "Structural Inorganic Chemistry," Oxford, 1945, p. 139). These results have led to the general aceptance of a halogen bridge structure (I) for this dimer. The properties of ferric chloride make it inconvenient for a study of the properties of the bridge because of the ease with which it undergoes hydrolysis, but it was hoped that by using a chelate group the bridge could be stabilised with the formation of an octahedral complex as in (III). Tertiary arsines, and tertiary phosphines, are specially convenient for investigations of this nature, for their complexes are usually soluble in organic solvents and so permit of determination of molecular weights; furthermore, these ligands have not the troublesome consequences which often arise from the basic nature of ammonia and amines.

When the diarsine (II) reacts with anhydrous ferric chloride dissolved in alcohol or benzene

a red colour immediately develops and a crimson precipitate is obtained. The presence of a little water does not affect the reaction, which is very sensitive, the red colour being formed with only traces of ferric chloride, and under the right conditions precipitation of the ferric iron is almost quantitative. The *compound* has the empirical formula $FeCl_3.C_6H_4(AsMe_2)_2$; it melts at 219°, and dissolves readily in nitromethane, acetone, and nitrobenzene. The molecular weight was determined ebullioscopically in acetone and cryoscopically in nitrobenzene and some association was observed, x in the formula $[FeCl_3.C_6H_4(AsMe_2)_2]_x$ being found to vary between 1·1 and 1·4 according to the solvent and the concentration. The compound is stable in air and does not react with moisture unless dissolved in acetone and treated with a fairly large amount of water, whereupon hydrolysis takes place. The corresponding *bromide* has been prepared and has a deep chocolate-brown colour; it melts at 209° and has properties similar to those of the chloride except that it is very much less stable to water, which converts it very readily into the green *salt* $[FeBr_2.2C_6H_4(AsMe_2)_2]^+ Br^-$. The facts that both the chloride and the bromide melted and dissolved in certain organic solvents at first seemed to exclude a salt-like structure, and a bridged structure (III) seemed likely since dissociation of halogen bridges in the solvents used for the molecular weights is not uncommon. However, it was not possible to split the bridge with such co-ordinating groups as pyridine, triethylarsine, or *p*-toluidine, and the magnetic measurements were difficult to interpret on such a hypothesis.

Magnetic-susceptibility measurements showed that both the chloride and the bromide were strongly paramagnetic, with an effective magnetic moment of about 4·6 Bohr magnetons both in the solid state and in acetone solution. This value would correspond to between three and four unpaired electrons if it is assumed that the whole of the moment may be attributed to spin alone. Pauling ("Nature of the Chemical Bond," N.Y., 1945, 2nd edition, p. 115) predicts that a moment of 1·73 B.M. should be found for octahedral covalent complexes of ferric iron using d^2sp^3 bonds, owing to the presence of one unpaired electron in the 3*d* shell; an example of this type of complex is potassium ferricyanide, for which the moment of 2·33 B.M. has been reported, the larger value being accounted for by orbital contribution. On the other hand, ionic complexes of ferric iron have a predicted magnetic moment of 5·92 B.M. due to the presence of five unpaired electrons; an example of this type of complex is the salt $(NH_4)_3FeF_6$ for which a moment of 5·9 B.M. has been reported. In Table I are shown the electronic

TABLE I.

Calculated magnetic moments for various types of iron complexes.

Complex.	Electronic arrangement. 3*d*.	4*s*.	4*p*.	Calculated * magnetic moment (μ).
Ferric covalent octahedral (d^2sp^3 bonds)	↓↑ ↓↑ ↓↑	↓↑	↓↑ ↓↑ ↓↑	1·73
Ferric ionic, octahedral or tetrahedral ...	↓ ↓ ↓ ↓ ↓			5·92
Ferric covalent planar (dsp^2 bonds)	↓↑ ↓ ↓ ↓↑	↓↑	↓↑ ↓↑	3·88
Ferrous covalent octahedral (d^2sp^3 bonds)	↓↑ ↓↑ ↓↑	↓↑	↓↑ ↓↑ ↓↑	0·00
Ferrous ionic, octahedral or tetrahedral	↓↑ ↓ ↓ ↓			4·90
Ferrous covalent planar (dsp^2 bonds).....	↓↑ ↓↑ ↓ ↓↑	↓↑	↓↑ ↓↑	2·83

* These values are calculated on the assumption that the whole of the moment is due to spin alone. Usually, there is a small orbital contribution which increases these values slightly; its effect is most marked with the lower values.

arrangements and calculated magnetic moments for various types of ferrous and ferric complexes. The most unusual value of 4·6 B.M. for the complexes described above would be found in compounds in which both covalent and ionic binding were present, and with this idea in mind alternative methods for formulating these complexes were examined.

If it be assumed that the compounds are salts, the formulæ $[Fe(C_6H_4(AsMe_2)_2)_2][FeCl_4]$ and $[Fe(C_6H_4(AsMe_2)_2)_2Cl_2][FeCl_4]$ are possibilities. The former would contain the most unlikely

square co-ordinated ferric iron, the cation having three and the anion five unpaired electrons (see Table I). The second formula, however, contains one octahedrally co-ordinated ferric atom, which would contain one unpaired electron if covalent bonds are present, and one ferric atom in which five unpaired electrons are expected; it will be shown that the susceptibility found is almost exactly that calculated for the second formula. This structure has also been confirmed by the preparation of the *perchlorate* of the cation. When an acetone solution of the *chloride* is treated with perchloric acid, a red precipitate is immediately formed, which has the formula $[Fe\{C_6H_4(AsMe_2)_2\}_2Cl_2][ClO_4]$. This compound has a magnetic moment of 2·34 B.M., which indicates one unpaired electron if due allowance is made for the orbital contribution, and shows that the cation is an octahedrally co-ordinated complex of ferric iron with covalent bonds. The magnetic susceptibilities of the various compounds are shown in Table II.

TABLE II.

Experimental magnetic susceptibilities of iron complexes.

Compound.	$\chi_M \times 10^{-6}$ (20°).	Diamagnetic correction.	$\chi_M \times 10^{-6}$ corr. for diamagnetism.	Magnetic moment (μ) per Fe atom.
1. $[Fe(Diarsine)_2Cl_2][FeCl_4]$	16,950	523	17,470	4·55
2. $[Fe(Diarsine)_2Cl_2][ClO_4]$	1,860	461	2,320	} 2·34
3. $[Fe(Diarsine)_2Cl_2]^+$	1,890	431	2,320	
4. $[FeCl_4]^-$ (from (1)–(3))	15,060	94	15,150	5·98
5. $[Fe(Diarsine)_2Br_2][FeBr_4]$	17,100	598	17,700	4·57

(The diamagnetic corrections used in this table were taken from Selwood, "Magnetochemistry," N.Y., 1943, p. 52.)

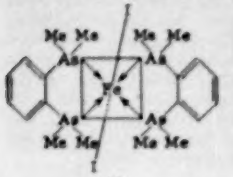
By subtracting the susceptibility of the chlorate ion from the susceptibility of the salt (2) (Table II), we obtain the susceptibility of the $[Fe(Diarsine)_2Cl_2]^+$ cation. If this value be then subtracted from the susceptibility of the compound (1) we obtain the susceptibility of the $[FeCl_4]^-$ ion and the magnetic moment calculated from this (μ = 5·98 B.M.) is in good agreement with that calculated for ferric iron with ionic bonds (μ = 5·92).

The behaviour of the ferric bromide *complex* (5) with water is readily explained from a consideration of its structure, for the first step one would expect is hydrolysis of the $[FeBr_4]^-$ ion; the product, $[Fe(Diarsine)_2Br_2]Br$, can be isolated because of its fairly low solubility in aqueous acetone. The corresponding chloride complex could not be isolated. The addition of a considerable amount of water to an acetone solution of the chloride (1) caused no change in colour or any immediate precipitate, although on long standing a brownish precipitate consisting chiefly of ferric hydroxide was obtained, which indicated complete breakdown of the compound. It is quite possible that the compound $[Fe(Diarsine)_2Cl_2]Cl$ is too soluble to be isolated under the conditions employed. The solubility of a salt like $[Fe(Diarsine)_2Cl_2][FeCl_4]$ in acetone, nitrobenzene, and nitromethane is explained by the high dielectric constants of these liquids; in spite of the large organic molecules which go to make up their structure, these compounds are quite insoluble in benzene and chloroform, and their solubility in such good ionising solvents as those mentioned above must be taken as a significant indication of their structure. The molecular weights which are found in nitrobenzene and acetone show that the molecules are largely ionised in these solvents.

The failure to obtain a stabilised halogen-bridge complex with this diarsine chelating group seems to indicate that such octahedral bridged complexes must be most unstable. The conditions used appeared most favourable for the formation of such a compound; if ferric chloride exists in benzene as a halogen-bridged molecule, then addition of the chelate might be expected to give the bridged octahedral complex readily, since addition of the diarsine would merely involve increasing the co-ordination number of the ferric atom from four to six without affecting the bridge.

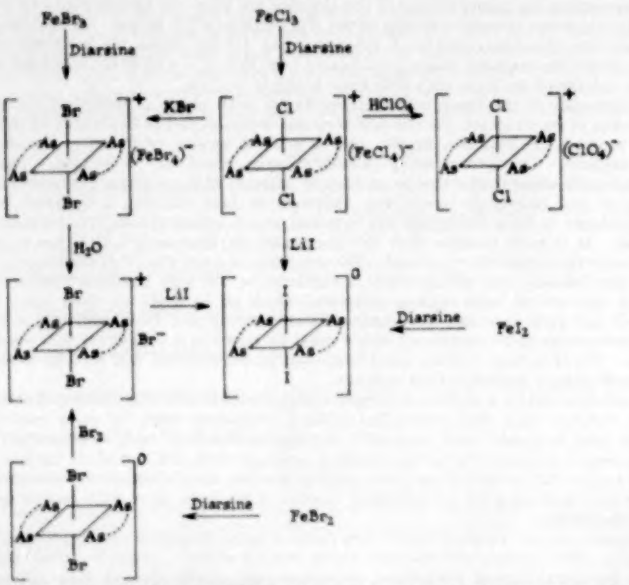
Attempts to isolate the ferric iodide salts resulted in the formation of a non-ionic complex of ferrous iron. The reaction between ferric iodide and the diarsine cannot be carried out directly owing to the instability of the former, so replacement of the chlorine from the compound $[Fe(Diarsine)_2Cl_2][FeCl_4]$ by the addition of lithium iodide in acetone solution was attempted. The dark solution quickly precipitated a yellow compound of empirical formula $Fe(Diarsine)_2I_2$ which was slightly soluble in acetone and chloroform, but solubilities were too low to enable one to carry out a molecular-weight determination. Since the compound is found to be diamagnetic, formulation as a planar four-covalent salt of the type $[Fe(Diarsine)_2]^{++}\ I^-_2$ is clearly excluded

because the use of dsp^2 bonds would require the presence of two unpaired electrons, making the compound paramagnetic (see Table I). The *compound* is thus a six-covalent non-ionic octahedral complex of ferrous iron with d^2sp^3 bonds (IV). This compound is one of the few examples known of diamagnetic, octahedral, non-ionic ferrous complexes; salt-like diamagnetic complexes of ferrous iron included the well-known red tris-o-phenanthroline and trisdipyridyl compounds. This compound appears to arise from the self-oxidation and -reduction of the unstable salt $[Fe(Diarsine)_2I_2]^+ I^-$, for the solution at first turns black on treatment with lithium iodide and then lightens and precipitates the ferrous complex. This black colour is also observed when a suspension of $[Fe(Diarsine)_2I_2]$ in alcohol is treated with iodine; a black precipitate is formed but the compound decomposed during attempts at its isolation. The ferrous complex may also be prepared by shaking together ferrous iodide and the diarsine in aqueous-alcoholic solution, the yellow ferrous iodide complex being quickly precipitated. The corresponding ferrous bromide complex may be prepared in a similar way and is also diamagnetic. When treated with bromine water, the ferrous bromide complex turns green immediately, with formation of the ferric salt $[Fe(Diarsine)_2Br_2]^+ Br^-$. The corresponding ferrous chloride complex was not isolated, but on shaking together a mixture of ferrous chloride and the diarsine in aqueous alcohol an immediate red colour was observed, and in the presence of air a copious precipitate of the ferric compound $[Fe(Diarsine)_2Cl_2][FeCl_4]$ was formed in a short time. In attempts to prepare a ferric thiocyanate complex the ferrous *compound* $[Fe(Diarsine)_2(CNS)_2]^0$ was



(IV.)

TABLE III.



isolated and, like the bromide and iodide, this compound is also diamagnetic and clearly an octahedral covalent complex. As with the iodide, reduction took place, and this is not difficult to understand in view of the oxidation potentials of the halogens; the oxidation potential for the reaction $2CNS^- \longrightarrow (CNS)_2$ (+0·77 v.) is much less than that for the reaction $2Br^- \longrightarrow Br_2$ (+1·07 v.) and not much more than that for the reaction $2I^- \longrightarrow I_2$ (+0·53 v.). Thus

the order of stability to oxidation of the ferrous complexes is iodide > thiocyanate > bromide > chloride, which is the order of increasing oxidation potentials of the halogens.

In Table III are shown the relationships between the various complexes of ferrous and ferric iron. In all cases the two halogen atoms are shown as *trans*- for convenience; this is probably the case but no attempt has been made to prove it.

Experimental.

o-Phenylenebisdimethylarsine.—This was prepared by the method of Chatt and Mann (*J.*, 1939, 610). From *o*-nitroaniline (414 g.) after the six steps a yield of 22·6 g. of the diarsine, b. p. 157°/14 mm., was obtained (Found: C, 42·2; H, 5·4. Calc. for $C_{10}H_{16}As_2$: C, 42·0; H, 5·6%) as a colourless oil of unpleasant odour; it was kept sealed. Unlike the trialkylarsines, it is not readily oxidised in air and is more stable to air than phenyldimethylarsine.

Dichloro(o-phenylenebisdimethylarsine)iron(III) *Tetrachloroferrate.*—Anhydrous ferric chloride (1·7 g.) was dissolved in purified spirit (75 ml.), and the solution filtered from traces of impurity and added with stirring to *o*-phenylenebisdimethylarsine (2·9 g.) dissolved in purified spirit (80 ml.). A crimson precipitate was immediately formed which was allowed to settle for about five minutes then filtered off and well washed with purified spirit, in which it was only very slightly soluble. An almost quantitative yield (4·5 g.) was obtained [Found: C, 26·6; H, 3·7; Cl, 23·5; Fe, 12·6%; *M* (cryoscopic) in 2·55% solution in nitrobenzene, 490; (ebullioscopic) in 2·76% solution in acetone, 536; in 3·67% solution in acetone, 637. $C_{20}H_{32}Cl_6As_4Fe_2$ requires C, 26·76; H, 3·6; Cl, 23·7; Fe, 12·48%; *M*, 897], m. p. 219° (decomp.). The *compound* was recrystallised from acetone–light petroleum. It dissolved readily in acetone, nitrobenzene, and nitromethane, was slightly soluble in alcohol and ethyl acetate, but completely insoluble in benzene, chloroform, ether, dioxan, and water. The compound was quite unaffected by water at room temperature. It could be prepared conveniently, also, by mixing solutions of the diarsine and ferric chloride dissolved in benzene, the crimson precipitate appearing immediately. The complex was stable indefinitely in air and no smell of arsine developed after many months' exposure to the atmosphere. Treatment of an acetone solution with silver nitrate solution caused decomposition of the compound, silver chloride being at once precipitated, and the colour changing from red to a deep blue which faded in about ½ hour. The substance responsible for this blue colour was not identified because of the rapid decomposition. When the acetone solution of the complex was treated with 1 mol. of pyridine, *p*-toluidine, or triethylarsine per iron atom there was no change in colour and the complex could be recovered unchanged by concentrating the solution. An acetone solution was not reduced by sulphur dioxide, but addition of perchloric acid to it gave an immediate precipitate of the perchlorate (see below).

Magnetic susceptibility. Magnetic susceptibilities were measured by the Gouy method on the magnet described by Baddar, Hilal, and Sugden (*J.*, 1949, 132). (*a*) The data for the powdered compound at 20° are in Table II; at 18·6°, $\chi = 18·8 \times 10^{-6}$, whence, after correction as before, $\mu = 4·52$; at 28·5°, $\chi = 18·4 \times 10^{-6}$, whence, after correction, $\mu = 4·55$.

(*b*) In acetone solution (*M*/25): at 23·8°, $\chi = 19·7 \times 10^{-6}$, $\chi_M = 17,600 \times 10^{-6}$, and after correction, mean $\mu = 4·61$; at 25·2°, $\chi = 20·0 \times 10^{-6}$, $\chi_M = 18,000 \times 10^{-6}$, and after correction, mean $\mu = 4·71$.

Dibromodi-(o-phenylenebisdimethylarsine)iron(III) *Tetrabromoferrate.*—*o*-Phenylenebisdimethylarsine (1·6 g.), dissolved in alcohol (100 ml.), was slowly added with rapid stirring to a freshly filtered solution of anhydrous ferric bromide (5 g.) dissolved in alcohol (30 ml.). (The ferric bromide was present in considerable excess and the order of addition given was followed to minimise formation of the green compound $[FeBr_2.2C_6H_4(AsMe_2)_2]Br$ described below.) A brown precipitate was formed immediately, and this was filtered off and washed many times with alcohol to remove excess of ferric bromide and any of the green compound, which is soluble in alcohol. The filtrate was finally very pale green owing to the presence of a small amount of the green compound formed by hydrolysis. The *tetrabromoferrate* (3·3 g., nearly quantitative) [Found: C, 20·8; H, 3·0; Br, 41·3; Fe, 9·7%; *M* (cryoscopic) in 2·73% solution in nitrobenzene, 692; (ebullioscopic) in 4·24% solution in acetone, 820; in 6·42% solution in acetone, 850. $C_{20}H_{32}Br_6As_4Fe_2$ requires C, 20·6; H, 2·58; Br, 41·25; Fe, 9·6%; *M*, 1164] was purified by recrystallisation from acetone–light petroleum. It dissolved readily in acetone, nitrobenzene, and nitromethane, forming a solution which was brown if dilute and red when concentrated. The compound formed brown shimmering crystals, m. p. 207° (decomp.), which under the microscope were seen to consist mainly of flat rhombs. The compound was completely insoluble in benzene, chloroform, ether, dioxan and organic solvents other than those mentioned above. Although it is insoluble in water it slowly hydrolysed to form the green salt $[FeBr_2(Diarsine)_2]Br$ and this green compound was also formed when water was added to a solution of the compound in acetone. An acetone solution of the complex reacted immediately with silver nitrate solution to precipitate silver bromide, the solution first turning green, then blue; the colour faded entirely in about 15 minutes.

Magnetic susceptibility. At 20°, see Table II. At 27·3°, $\chi = 14·3 \times 10^{-6}$, whence, after correction, mean $\mu = 4·57$.

Dibromodi-(o-phenylenebisdimethylarsine)iron(III) *Monobromide.*—Anhydrous ferric bromide (2 g.) was dissolved in alcohol (30 ml.), and the solution filtered and added with vigorous stirring to a solution of *o*-phenylenebisdimethylarsine (1·0 g.) dissolved in alcohol (75 ml.). A green compound was precipitated in a dark solution and a small amount of the brown ferribromide complex was formed also. The green precipitate had a characteristic appearance as shimmering, finely divided crystals. The mixture was then treated with distilled water with vigorous stirring until the brown colour disappeared, leaving only a green precipitate in a green solution. The solution was filtered quickly and the compound washed several times, first with small quantities of aqueous alcohol and finally with water. The minimum quantity of alcohol had to be used because of the high solubility of the compound in this solvent. After a final washing with light petroleum, the *compound* was obtained as microcrystalline

rods. Recrystallisation was difficult, for attempts at purification from acetone–light petroleum gave the brown ferribromide; also, contact with water for very long caused hydrolysis. The compound was nevertheless obtained fairly pure by starting with freshly filtered solutions and filtering rapidly after treatment with water. It probably still contained traces of ferric hydroxide formed by hydrolysis, as shown by the iron value (Found: C, 27·6; H, 3·7; Br, 27·3; Fe, 6·7. $C_{36}H_{88}Br_3As_6Fe$ requires C, 27·7; H, 3·7; Br, 27·7; Fe, 6·5%). The compound dissolved readily in alcohol, acetone, and warm water to a green solution. Boiling with insufficient alcohol to dissolve it caused some formation of the brown complex. It was practically insoluble in all other organic solvents. Treatment of an alcoholic solution with silver nitrate solution gave an immediate precipitate of silver bromide followed by development of a blue colour which faded rapidly.

Dichlorodi-(o-phenylenebisdimethylarsine)iron(III) *Perchlorate*.—The tetrachloroferrate (2·8 g.), prepared as above, was dissolved in acetone, and the solution filtered and treated at once with excess of perchloric acid (30%). The solution was well stirred and almost immediately a red crystalline precipitate of the *perchlorate* was obtained. This was filtered off after a few minutes and well washed with alcohol, in which it is practically insoluble. It was then dried in a vacuum desiccator, yield 2·0 g. [Found: C, 20·3; H, 4·3; Cl, 8·8; Fe, 7·0. $C_{36}H_{88}O_8Cl_2As_6Fe$ requires C, 30·1; H, 4·0; Cl, 8·9 (excluding Cl present in the ClO_4 ion), Fe, 7·0%]. It was slightly soluble in acetone and fairly soluble in nitrobenzene, but quite insoluble in water or organic solvents like chloroform or benzene. When heated the compound did not melt but decomposed violently about 210°.

Magnetic susceptibility. See Table II.

Di-iododi-(o-phenylenebisdimethylarsine)iron(II).—The tetrachloroferrate complex (1·35 g.), dissolved in acetone (70 ml.) and filtered from traces of impurity, was treated with lithium iodide (2 g.; excess) dissolved in acetone (30 ml.). The red solution immediately became dark brownish-red and finally brown. After 3 minutes' vigorous stirring, golden-yellow crystals were precipitated. These were filtered off, well washed with acetone, a little water, then finally with alcohol, and dried in a vacuum desiccator; yield 0·7 g. (Found: C, 27·2; H, 3·7; I, 29·3; Fe, 6·7. $C_{36}H_{88}I_2As_6Fe$ requires C, 27·2; H, 3·6; I, 28·8; Fe, 6·4%), a little more of the *complex* remaining dissolved in the acetone. In all other solvents the complex was quite insoluble. An acetone solution gave a precipitate with silver nitrate solution on warming. When heated the compound did not melt but began to darken at 250° and decomposed above 300°. This compound could also be prepared by shaking together for a few minutes an alcoholic solution of the arsine with an aqueous solution of ferrous iodide.

Magnetic susceptibility. $\chi = -0{\cdot}3 \times 10^{-6}$ whence $\mu = 0$.

Dibromodi-(o-phenylenebisdimethylarsine)iron(II).—Ferrous sulphate heptahydrate (0·6 g.) and sodium bromide (0·8 g.) were dissolved in air-free distilled water (20 ml.) containing one drop of 10*N*-hydrochloric acid and added to a solution of *o*-phenylenebisdimethylarsine (1·0 g.) dissolved in alcohol (20 ml.). Most of the arsine was immediately precipitated as an oil, and the solution developed a pale green colour owing to the presence of a little ferric salt. The mixture was well shaken in a 100-ml. stoppered flask for about ½ hour with frequent warming on the water-bath; most of the arsine had then dissolved and a yellow precipitate had started to form. After 24 hours with occasional shaking and heating, the residue was filtered off and well washed, first with alcohol and finally with distilled water until the washings gave no precipitate with silver nitrate. After a final washing with alcohol it was dried in the vacuum desiccator. The bright yellow *complex* (Found: C, 31·5; H, 4·6; Br, 20·5; Fe, 7·0. $C_{36}H_{88}Br_2As_6Fe$ requires C, 30·4; H, 4·1; Br, 20·2; Fe, 7·1%) was slightly soluble in alcohol and chloroform but could not be recrystallised. It was quite insoluble in all other common solvents. The alcoholic solution reacted with silver nitrate on warming. Bromine immediately oxidised the complex to the green ferric salt $[FeBr_2.2C_6H_4(AsMe_2)_2]Br$. On heating, the compound did not melt but decomposed near 300. It was diamagnetic but the susceptibility was not measured precisely because the yield (0·9 g.) was insufficient to fill the tube; the susceptibility was estimated at about $-0{\cdot}2 \times 10^{-6}$.

Dithiocyanatodi-(o-phenylenebisdimethylarsine)iron(II).—Anhydrous ferric chloride (1·6 g.) was dissolved in absolute alcohol (100 ml.), and the solution filtered and treated with a solution of ammonium thiocyanate (2·8 g.) in absolute alcohol (100 ml.). To the dark red solution was added *o*-phenylenebisdimethylarsine (2·9 g.) dissolved in absolute alcohol (50 ml.). The solution was well stirred and left for 5 minutes, a heavy purple powder being precipitated. This was filtered off and washed many times with absolute alcohol until the washings showed only a very pale green colour. After a final washing with water the *compound* was dried in the vacuum desiccator; yield, 3·1 g.; m. p. 293° (decomp.) (Found: C, 35·6; H, 4·4; N, 3·7; S, 8·6; Fe, 7·6. $C_{38}H_{88}N_2S_2As_6Fe$ requires C, 35·4; H, 4·3; N, 3·76; S, 8·6; Fe, 7·5%). This powder had a magnetic susceptibility of $+0{\cdot}17 \times 10^{-6}$ but after recrystallisation from chloroform and light petroleum this value fell to $0{\cdot}0 \times 10^{-6}$; the higher initial value was probably due to traces of ferric salt. The compound was slightly soluble in acetone and chloroform to a purple solution but was insoluble in water, benzene, light petroleum, and other common solvents. An acetone suspension reacted very slowly with silver nitrate to precipitate silver thiocyanate. When heated, the compound became lighter in colour above 200°. When finely divided the complex had a purplish-pink colour.

The author gratefully acknowledges valuable discussions with Dr. J. Chatt and Dr. D. P. Craig and technical assistance in the preparation of the diarsine from Mr. T. J. Collins. The award by the University of London of an I.C.I. Fellowship, during the tenure of which this work was carried out, is also acknowledged. The author is indebted to Professor C. K. Ingold, F.R.S., for his interest in this work.

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, November 7th*, 1949.]

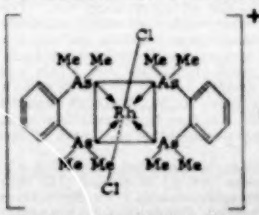
173. *Studies in Co-ordination Chemistry. Part IV. Complexes of Rhodic Halides with a Ditertiary Arsine.*

By R. S. Nyholm.

The complexes of tervalent rhodium halides with a chelating ditertiary arsine, *o*-phenylenebisdimethylarsine, have been prepared and studied. A series of salts have been isolated in which the univalent cation contains two molecules of the chelate group co-ordinated to the rhodium atom, two halogen atoms completing the octahedral configuration. All attempts to obtain complexes in which a halogen bridge connected two rhodium atoms were unsuccessful and it is concluded that such bridges, if formed, are unstable. The properties of the complexes are discussed.

In view of the ease with which bivalent rhodium formed binuclear halogen bridged complexes with tertiary arsines (Dwyer and Nyholm, *J. Proc. Roy. Soc. N.S.W.*, 1941, **75**, 127), the preparation of similar complexes of tervalent rhodium has been attempted. With tertiary arsines, bivalent rhodium halides gave rise to binuclear halogen bridged complexes of the type $[Rh(Hal)_2.3AsR_3]_2$ very readily and it was hoped that favourable circumstances for bridge formation with tervalent rhodium would be provided by the use of a suitable ditertiary arsine chelating group. Earlier work with diphenylmethylarsine (Dwyer and Nyholm, *ibid.*, p. 140) had shown that non-electrolytes of the formula $Rh(Hal)_3.3AsR_3$ could be isolated, but the use of a ditertiary arsine chelating group forces the rhodium either to bridge or to form a salt to complete a co-ordination number of six. It has been found, however, that the only complexes which could be isolated were salts containing two molecules of the chelate group to each rhodium atom and in which only part of the halogen was ionised. Variations in the method of preparation, such as changing the ratio of the reactants or refluxing the rhodium bisdiarsine salt with excess rhodic halide, failed to give the dimer. If formed, this dimer should be easily isolated, for binuclear complexes are usually much less soluble than the monomers from which they are derived. Most Group VIII metals, particularly those of the palladium and the platinum triad, have a tendency to form non-electrolytes with tertiary arsines rather than salts, and the formation of a salt in this case suggests that halogen bridges between tervalent rhodium atoms, if formed, are weaker than those between bivalent rhodium atoms.

The compounds isolated had the general formula $Rh(Hal)_3.2C_6H_4(AsMe_2)_2$; the chloride was investigated more than the *bromide* or the *iodide* because of its higher solubility in water, but the other two salts had similar properties. The compounds were formed in solution by heating the diarsine under reflux with the appropriate rhodic salt and were precipitated by addition of the corresponding acid. Since only part of the halogen was ionised, a salt-like structure for the complexes was presumed; then if a co-ordination number of six for the rhodium is assumed, the structure $[Rh(Hal)_2.2C_6H_4(AsMe_2)_2]Hal$ was expected. In the case of the chloride, this is as inset, the rhodium atom being octahedrally co-ordinated and the compound is ***dichlorodi-(o-phenylenebisdimethylarsine)-rhodium*(III) *chloride***. This formulation has been confirmed by conductivity measurements and potentiometric titration with silver nitrate, a silver electrode being used. The molecular conductivity at a dilution of 1024 litres was 94 mhos; this figure is of the order expected for a strong electrolyte which forms two ions per molecule. The M/1024-solution was then titrated with silver nitrate in the presence of acetone and barium nitrate; the acetone was used to increase the sensitivity, and the barium nitrate the conductivity. The end-point of the titration occurred after only one of the three chlorine atoms had been precipitated (see figure), showing that only one chlorine atom was ionised. The small divergence from the calculated value is attributed to slight hydrolysis of the two covalently bound halogen atoms. In view of the dilution, the smallness of this hydrolysis is remarkable and indicates a very stable cation.



There is no evidence as to whether the two covalently bound chlorine atoms in the complex cation are *cis*- or *trans*-, but the latter is considered the more likely. This could be decided by attempts at optical resolution, for the *cis*-dichloro-compound should be capable of being resolved, but the *trans*-complex is inactive for it has a plane of symmetry. Complexes of tervalent cobalt and nickel in which similar cations are present will be described in Parts V and VI of this series.

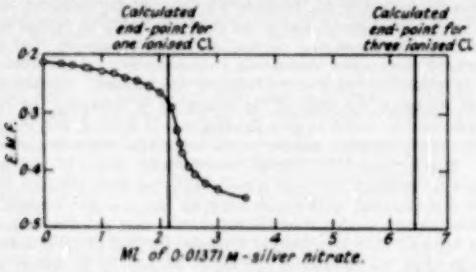
Experimental.

o-Phenylenebisdimethylarsine.—This was prepared as described in Part III (preceding paper).

Dichlorodi-(o-phenylenebisdimethylarsine)rhodium(III) *Monochloride.*—Sodium hexachlororhodate (0·65 g.), dissolved in distilled water (10 ml.), was treated with *o*-phenylenebisdimethylarsine (0·45 g.) in alcohol (70 ml.) containing hydrochloric acid (10*N*.; 5 ml.). (The ratio Rh : arsine was 1 : 1 in an attempt to obtain the bridged complex.) When the solution was heated, all the arsine dissolved, and after a few minutes the colour changed from red to light yellow, the complex salt being formed in solution. (An atmosphere of hydrogen, used initially, was later found unnecessary.) The solution was then heated under reflux for many hours in an attempt to effect bridging, but the only reaction was partial reduction to rhodium. The solution was filtered, and the filtrate concentrated to about 10 ml. and treated with concentrated hydrochloric acid. A yellow precipitate was obtained immediately and after cooling in ice this was filtered off and washed quickly with ice-cold dilute alcoholic hydrochloric acid and finally with small quantities of ice-cold water. It was then dried in the vacuum desiccator giving a yield of 0·4 g. The *compound*, recrystallised from aqueous alcohol containing a little hydrochloric acid, decomposed above 300° without melting (Found: C, 30·4; H, 4·2; Cl, 13·6; Rh, 13·1. $C_{36}H_{44}Cl_3As_4Rh$ requires C, 30·7; H, 4·1; Cl, 13·6; Rh, 13·1%). It was completely insoluble in benzene, chloroform, or light petroleum but dissolved readily in acetone or alcohol and was moderately soluble in warm water.

During the above preparation one occasionally obtained a heavy brown precipitate after a few seconds' refluxing which gradually re-dissolved on further heating. It was quite insoluble

Potentiometric titration of M/1024-$[RhCl_2.2C_6H_4(AsMe_2)_2]Cl$, *with silver–silver chloride electrode.*



in all solvents and was probably the complex *salt* $[RhCl_2.2C_6H_4(AsMe_2)_2]_2[RhCl_4]$ (Found: Rh, 16·0. $C_{36}H_{44}Cl_{12}As_8Rh_3$ requires Rh, 16·2%). This compound appears to arise from the temporary coexistence of the two necessary ions, and it is significant that it is formed most readily in the presence of excess of sodium hexachlororhodate.

Dibromodi-(o-phenylenebisdimethylarsine)rhodium(III) *Bromide.*—Sodium hexachlororhodate (1·0 g.), dissolved in distilled water (13 ml.), was added to *o*-phenylenebisdimethylarsine (1·45 g.) in alcohol (60 ml.) containing concentrated hydrobromic acid (5 ml.); 30% hypophosphorous acid (2 ml.) was added to prevent the formation of bromine; it caused very little reduction of the rhodium salt. The solution was heated, and after a few minutes a brown sandy powder was precipitated which gradually dissolved on further refluxing to form an orange solution. After several hours' refluxing the solution was filtered from a very small amount of precipitate and concentrated to a small bulk on the water-bath. On cooling the residue (about 15 ml.) in ice, a yellowish-brown powder crystallised out. This was filtered off and washed with ice-cold alcohol and finally with ice-cold distilled water. It was dried in a vacuum desiccator. The *compound* (Found: C, 27·0; H, 3·8; Rh, 11·4. $C_{36}H_{44}Br_2As_4Rh$ requires C, 26·2; H, 3·5; Rh, 11·25%) did not melt but decomposed above 300°. It may be recrystallised from alcohol containing a little hydrobromic acid. An alcoholic solution precipitated only part of the bromine on treatment with silver nitrate.

Di-iododi-(o-phenylenebisdimethylarsine)rhodium(III) *Iodide.*—Sodium hexachlororhodate (2·0 g.), dissolved in water (25 ml.), was added to *o*-phenylenebisdimethylarsine (2·9 g.) in alcohol (125 ml.) containing hydriodic acid (57%; 10 ml.) just decolorised with hypophosphorous acid. To the mixture was added hypophosphorous acid (4 ml.), and on heating, the arsine quickly dissolved and a brownish-red powder was precipitated. This gradually dissolved on further refluxing and after 2 hours the solution was filtered and heated on the water-bath until the volume was about 50 ml. On cooling, beautiful crimson crystals were precipitated which were filtered off and washed many times with alcohol and finally with water. The *iodide* was much less soluble than the chloride or bromide and the addition of hydriodic acid when recrystallising from alcohol was not necessary. Two recrystallisations from alcohol gave an analytically pure specimen (Found: C, 23·0; H, 3·2; I, 36·2; Rh, 9·8. $C_{36}H_{44}I_2As_4Rh$ requires C, 22·7; H, 3·0; I, 36·2; Rh, 9·75%). The compound was completely insoluble in all organic solvents except alcohol and was insoluble in water. An alcoholic solution gave an immediate precipitate with silver nitrate, more silver iodide being formed on boiling owing, apparently, to rupture of the cation.

Conductivity of the Chloride Complex.—Measurements were carried out in a pipette-type cell of volume about 15 ml. and constant 0·0508 $cm.^{-1}$. The resistance of an M/1024-solution of the salt in this cell

at 25° was 532 ohms. The conductivity of the water used was $3\cdot5 \times 10^{-6}$ mho/cm.^{3}. From these data the molecular conductance at a dilution of 1024 litres is 94 mhos.

Potentiometric Titration.—30 Ml. of the M/1024-solution of the chloride complex were treated with AnalaR acetone (100 ml.) and barium nitrate (1 g.), and the solution titrated with 0·01371M-silver nitrate from a microburette, the solution being stirred vigorously throughout the titration. A silver–silver chloride electrode was immersed in the solution, and a reference electrode consisting of a silver–silver chloride electrode in saturated potassium chloride connected to the solution through an ammonium nitrate bridge. The result (see figure) shows clearly that only one of the three chlorine atoms is ionised.

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SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, November 7th*, 1949.]

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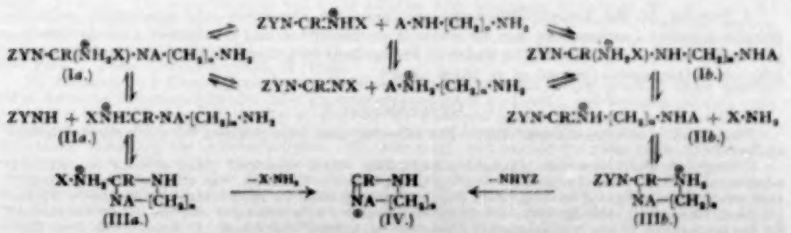
174. *Amidines. Part XIII. Preparation of 2-Substituted 4 : 5-Dihydroglyoxalines and Ring Homologues from Substituted Amidines and Alkylenediamines.*

By P. OXLEY and W. F. SHORT.

2-Substituted 4 : 5-dihydroglyoxalines and ring homologues are produced in good yield by heating substituted amidinium salts with an alkylenediamine. Ketoxime sulphonates and ethylenediamine also give 2-substituted 4 : 5-dihydroglyoxalines. Reaction mechanisms are proposed.

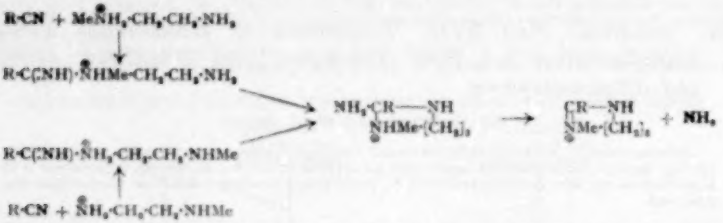
As a sequel to the investigation of the action of ammonia and monoamines on *N*-substituted amidinium salts and on ketoxime sulphonates (Parts IX and XI, *J.*, 1948, 1514; 1949, 449) we have examined the behaviour of these compounds with alkylenediamines. Miescher, Urech, Klarer, and Ciba (U.S.P., 2,252,721), Klarer and Urech (*Helv. Chim. Acta*, 1944, **27**, 1772), and Djerassi and Scholz (*J. Amer. Chem. Soc.*, 1947, **69**, 1688) have prepared a few 2-arylaminomethyl-, 2-hydroxymethyl-, and 2-aryloxymethyl-4 : 5-dihydroglyoxalines from ethylenediamine and the appropriate unsubstituted amidinium chloride in boiling alcohol, but the reaction of alkylenediamines with *N*-substituted amidines has not been investigated. We find that 2-substituted 4 : 5-dihydroglyoxalines and ring homologues are obtained in good yield by heating *N*-substituted amidinium salts with an alkylenediamine at temperatures within the range 50—180°. It is convenient to use the amidinium sulphonates, but chlorides, benzoates, and picrates have also been used. Aniline, nitrobenzene, and other solvents used in the ammonolysis of *N*-arylamidinium salts (Part XI, *loc. cit.*) could be employed in the reaction but were usually unnecessary. The amidine may have one, two, or three alkyl or aryl substituents on the nitrogen atoms, and the *N*-monoaryl derivatives are especially suitable owing to their ready availability (Part I, *J.*, 1946, 147; Part XI, *J.*, 1949, 449). The scope of the method is illustrated by the twenty-three examples in Table I, and it will be noted that *N*-alkylethylenediamines give 2-substituted 1-alkyl-4 : 5-dihydroglyoxalines. Since there is no reaction between an alkylenediamine and an *N*-substituted amidine at temperatures which yield a cyclic base when the amidinium salt is employed, it is probable that the reaction involves



the production of orthoamidinium ions (Ia and Ib) from the amidinium salt, ZYN·CR:NHX, and the alkylenediamine, A·NH·[CH$_2$]$_n$·NH$_2$, or from the reciprocal pair. The orthoamidinium

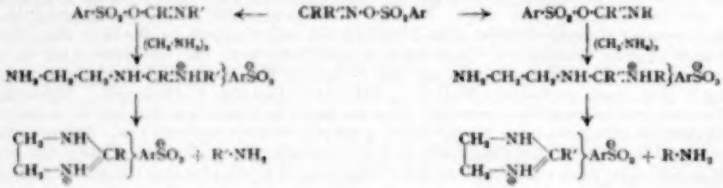
ions subsequently lose two molecules of amine (or one of ammonia and one of amine), as shown in the annexed scheme, representative of other routes in which the amines are eliminated in the reverse order and of structures with a different distribution of the positive charge. The intervention of cyclic compounds of the type (IIIa and *b*) is postulated since the dihydroglyoxaline resulting from the direct elimination of an amine from (IIb) would not necessarily contain the group A, whereas, in fact, 1-methyldihydroglyoxalines (IV; A = Me, n = 2), unaccompanied by the corresponding dihydroglyoxalines (IV; A = H, n = 2), are obtained from a substituted amidinium salt and *N*-methylethylenediamine.

The 2-arylmethyl-1-alkyl-4 : 5-dihydroglyoxalines enumerated in Table II were prepared by the interaction of the appropriate cyanide with a salt of *N*-methyl- or *N*-ethyl-ethylenediamine (Part VI, *J.*, 1947, 497), and the exclusive formation of dihydroglyoxalines containing a 1-alkyl group suggests the production of a cyclic intermediate which subsequently loses the elements of ammonia :



These *N*-alkyldihydroglyoxalines were examined by Gowdey (*Brit. J. Pharmacol.*, 1948, **3**, 254; 1949, **4**, 45) who found that, regardless of the action of the compounds not containing a *N*-substituent, they all cause a rapid rise of the blood-pressure and an increased heart-rate; moreover, the compounds unsubstituted on nitrogen affect the perivascular system directly whereas the *N*-alkyl derivatives affect the blood-pressure by a more central action, involving stimulation of the sympathetic ganglia, liberation of adrenaline, and direct action on the cardiac muscle.

Rearrangement of ketoxime sulphonates in presence of ethylenediamine gives 2-substituted dihydroglyoxalines, the ester of methyl ethyl ketoxime giving rise to both 2-methyl- and 2-ethyl-4 : 5-dihydroglyoxaline (compare Part IX, *J.*, 1948, 1514).



A number of the 1-methyldihydroglyoxalines were converted into quaternary salts for pharmacological examination, but an attempt to methylate and quaternise 1-benzyldihydroglyoxaline in one stage resulted in fission of the nucleus with formation of *N*-2-dimethylamino-ethylphenylacetamide (*picrate*, m. p. 165·5—166°).

Experimental.*

Preparation of Alkylenediamine Salts.—The following salts were prepared by the method described in Part VI (*J.*, 1947, 502).

N-Methylethylenediammonium ditoluene-p-sulphonate, which separated from ethanol in colourless needles, m. p. 176° (Found : N, 6·6. $C_{17}H_{24}O_6N_2S_2$ requires N, 6·7%), was obtained from *N*-methylethylenediamine, prepared in 42% yield from ethylenediamine by modification of Aspinall's method (*J. Amer. Chem. Soc.*, 1939, **61**, 822). Direct methylation of ethylenediamine was not a practical method for the preparation of the *N*-monomethyl derivative (cf. Linsker and Evans, *J. Amer. Chem. Soc.*, 1945, **67**, 1581). Attempts to prepare a crystalline monotoluene-*p*-sulphonate of the *N*-methyl base were unsuccessful.

* See also B.P. 614,032/1946.

N-Ethylethylenediammonium ditoluene-p-sulphonate, m. p. 158—159° (Found: N, 6·55. $C_{18}H_{24}O_6N_2S_2$ requires N, 6·5%) was prepared from *N*-ethylethylenediamine, obtained in 35% yield by Aspinall's method (*loc. cit.*).

Dihydroglyoxalines and Ring Homologues from N-Substituted Amidinium Salts and Alkylenediamines.—All the amidinium salts used in the experiments have been described in previous parts of the series. An equimolecular mixture of the *N*-substituted amidine, alkylenediamine, and acid (the last being introduced as free acid or as the amidinium, alkylenediammonium, or ammonium salt) was heated under the conditions recorded in Table I. Often no solvent was necessary, but reactions involving compounds of relatively high m. p. were facilitated by the addition of a small excess of alkylenediamine, or of a solvent such as aniline, dimethylaniline, or nitrobenzene. The salt of the heterocyclic base usually crystallised directly from the reaction mixture, but dilution with acetone or ether was occasionally necessary. One recrystallisation from methanol, isopropanol, or acetone was sufficient to give a product of constant m. p. The experiments recorded in Table I were conducted with 0·005—0·01 g.-mol. of the amidinium salt, and the yields are calculated on the amidine.

Preparation of 2-Substituted 1-Alkyl-4 : 5-dihydroglyoxalines.—Since dihydroglyoxalines and their 1-alkyl derivatives are of comparable basic strength, direct alkylation gives a mixture of dihydroglyoxaline, 1-alkyldihydroglyoxaline, and quaternary salt. The separation of this mixture is often laborious and yields are poor. Thus when 2-benzyl-4 : 5-dihydroglyoxaline (36 g.), methyl toluene-*p*-sulphonate (42 g., 1 mol.), and benzene (100 c.c.) were boiled for an hour, a heavy oil was obtained from which a mixture of 2-benzyl-4 : 5-dihydroglyoxaline and its 1-methyl derivative were liberated by 5*N*-sodium hydroxide. This mixture could not be satisfactorily separated into its constituents by distillation, but fractional crystallisation of the mixed picrates from methanol afforded hexagonal plates of 2-benzyl-1-methyl-4 : 5-dihydroglyoxalinium picrate, m. p. 125—125·5° (15·5 g., 17%), identical with that obtained by the alternative method (see Table II).

The 1-alkyldihydroglyoxalines described in Table II were prepared from the appropriate cyanide, *N*-alkylethylenediamine (1 mol.), and ammonium toluene-*p*-sulphonate (1 mol.), according to the method described in Part VI (*loc. cit.*). No unsubstituted dihydroglyoxalines were formed in this reaction, and the 1-alkyldihydroglyoxalines were very easily purified and obtained in good yield.

1 : 8-*Di*-(1-*methyl*-4 : 5-*dihydro*-2-*glyoxalinyl*)*octane*. A mixture of octamethylene dicyanide (8·2 g.), *N*-methylethylenediammonium ditoluene-*p*-sulphonate (20·9 g., 0·5 mol.), and *N*-methylethylenediamine (3·7 g., 0·5 mol.) was heated at 190° for 2 hours. Crystallisation of the crude product from isopropanol afforded 1 : 8-di-(1-methyl-4 : 5-dihydro-2-glyoxalinyl)octane ditolnene-*p*-sulphonate (16·6 g., 53%). The properties of this salt and of the dipicrate are recorded in Table II.

1 : 2-*Di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*ethane*. Benzyl cyanide (11·7 g.), **3 : 6-diazaoctane-1 : 8-diamine** ("triethylenetetramine") (7·3 g., 0·5 mol.), and ammonium toluene-*p*-sulphonate (18·9 g.; 1 mol.) were heated at 190° for 90 minutes. The resulting yellow gum was dissolved in water, made alkaline with 5*N*-sodium hydroxide, and extracted with chloroform. The light-brown residue (15 g.) obtained by evaporating the solvent was crystallised from benzene (15 c.c.) giving **1 : 2-*di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*ethane***, m. p. 131—132° (Found: N, 16·0. $C_{22}H_{26}N_4$ requires N, 16·2%) (7·5 g., 43%). The *dipicrate* had m. p. 235° (decomp.) (Found: N, 17·5. $C_{34}H_{30}O_{14}N_{10}$ requires N, 17·4%), and the *dihydrochloride*, obtained from the base and hydrogen chloride in isopropanol, separated as a crystalline powder, m. p. 275° (decomp.) (Found: N, 13·3. $C_{22}H_{28}N_4Cl_2$ requires N, 13·4%).

Dihydroglyoxalines from Ketoxime Sulphonates.—The ketoxime sulphonates were prepared as described in Part IX (*loc. cit.*).

2-*Phenyl*-4 : 5-*dihydroglyoxaline*. Ethylenediammonium dibenzenesulphonate, m. p. >360° (5·8 g., 32%), was deposited when benzophenone oxime benzenesulphonate (16·4 g.), anhydrous ethylenediamine (3 g., 1 mol.), and benzene (100 c.c.) were boiled for 1 hour and then cooled. The filtrate was washed with aqueous sodium hydroxide to remove benzenesulphonic acid, concentrated, and distilled on the steam-bath at 1 mm. to remove aniline (3 g., 64%). The residue consisted of *NN'*-diphenylbenzamidine, resulting from the action of aniline on the imidosulphonate produced by rearrangement of part of the oxime ester (Part IX, *loc. cit.*), and 2-phenyl-4 : 5-dihydroglyoxaline. Neutralisation of the mixture with aqueous benzenesulphonic acid afforded the sparingly soluble *NN'*-diphenylbenzamidinium benzenesulphonate, m. p. and mixed m. p. 218° (4 g., 19%), and 2-phenyl-4 : 5-dihydroglyoxaline, m. p. and mixed m. p. 101° (5·5 g., 77·5%), was isolated from the aqueous solution.

2-*Methyl*-4 : 5-*dihydroglyoxaline*. (i) Acetoxime benzenesulphonate (21·3 g.) ethylenediamine (6·0 g., 1 mol.), and toluene (50 c.c.) were boiled under reflux for ½ hour and the cold solution was extracted with water (25 c.c.). The aqueous layer was made alkaline with 5*N*-sodium hydroxide (50 c.c.), and the crude methyldihydroglyoxaline (7·9 g.) was collected in chloroform and converted into the picrate, m. p. 202° (24·0 g., 74·5%) with methanolic picric acid. Recrystallisation from water gave flat needles of 2-methyl-4 : 5-dihydroglyoxalinium picrate, m. p. and mixed m. p. 204° (Aspinall, *loc. cit.*; Chitwood and Reid, *J. Amer. Chem. Soc.*, 1935, **57**, 2424).

(ii) 2-Methyl-4 : 5-dihydroglyoxalinium benzenesulphonate was the major product when methyl ethyl ketoxime benzenesulphonate (22·7 g.), ethylenediamine (6 g., 1 mol.), and benzene (50 c.c.) were boiled for 1 hour, but a little 2-ethyl-4 : 5-dihydroglyoxalinium benzenesulphonate was also formed. The bases, b. p. 100—103°/18 mm. (5·9 g.), were obtained by shaking the product with 5*N*-sodium hydroxide, extracting the aqueous solution with chloroform, and uniting the chloroform and benzene solutions. A solution of the mixed bases and picric acid (15·5 g.) in methanol (80 c.c.) deposited a crude picrate, m. p. 190°, after 1 hour at 0°, and recrystallisation from methanol afforded 2-methyl-4 : 5-dihydroglyoxalinium picrate, m. p. and mixed m. p. 204° (15·2 g., 48·5%). The original filtrate was evaporated to dryness and the residue was recrystallised from isopropanol, giving 2-ethyl-4 : 5-dihydroglyoxalinium picrate, m. p. and mixed m. p. 135—136° (2·5 g., 7·5%).

Preparation of Quaternary Salts of Dihydroglyoxalines.—**2-*Benzyl*-1 : 3-*dimethyl*-4 : 5-*dihydroglyoxalinium salts*.** An aqueous solution of the oily product which separated when 2-benzyl-1-methyl-4 : 5-dihydroglyoxaline (16·2 g.), methyl toluene-*p*-sulphonate (17·5 g., 1 mol), and dry benzene (100 c.c.) were boiled for 15 minutes, was treated with 2*N*-lithium picrate, and the solid (26 g.; m. p. 115—118°)

TABLE I.

Preparation of 2-substituted 4 : 5-dihydroglyoxalines and ring homologues from substituted amidines.

Heterocyclic compound.						Alkylene-diamine (mols.).	Reaction: temp.	Reaction: time (mins.).
	Salt.*	M. p.	Yield, %.	Amidine.	Salt of amidine.*			
4 : 5-*Dihydroglyoxalines.*								
(1) 2-Methyl-	Picrate	204°	80	*N-cyclo*Hexyl-*N'*-ethyl-acet-	T	1·0	100°	30
(2) ,,	Picrate	204	88	*NN'*-Diphenylacet-	HCl	1·2	100	120
(3) 2-Ethyl-	Picrate	135—136	79	*NNN'*-Triethylpropion-	T	1·0	100	60
(4) 2-α-Butyl-	T	98	87	*N-p*-Tolylvaler-	T	1·33	100	30
(5) 2-Benzyl-	HCl	174	78	*N-cyclo*Hexylphenyl-acet-	HCl	1·7	*ca.* 180	5
(6) 2-*cyclo*Hexyl-	T *	171	97·5	*N*-Phenyl*cyclo*hexane-carboxy-	T	1·0	80	30
(7) 2-Phenyl-	T	165	73	*NNN'*-Trimethylbenz-	T	1·0	100	30
(8) ,,	Benzoate	115·5	77	*N*-Phenyl-*N'*-benzyl-benz-	Benzoate	1·0	100	30
(9) ,,	B	141	92	*NN*-Pentamethylene-*N'*-phenylbenz-	B	1·7	100	60
(10) ,,	B	141	87	*N*-Phenylbenz-	B	1·7	100	120
(11) ,,	T	164	91	*N*-Phenylbenz-	T	1·0	100	120
(12) 2-*p*-Methoxy-phenyl-	T	201	86	*N-p*-Tolyl-*p*-methoxy-benz-	T	1·7	100	120
(13) ,,	T	201	81	*N-p*-Tolyl-*p*-methoxy-benz-	T	1·7	140	60
(14) 2-*o*-Chloro-phenyl-	T *	163	88	*N*-Phenyl-*o*-chlorobenz-	T	1·0	140	30
(15) 2-3' : 4'-Di-methoxy-phenyl-	B *	192—192·5	88	*N*-Phenyl-3 : 4-di-methoxybenz-	B	1·5	100	60
(16) 2-2'-Naphthyl-	B *	188·5	82	*N-o*-Tolyl-2-naphth-	B	1·7	100	120
1-*Methyl*-4 : 5-*dihydroglyoxalines.*								
(17) 2-Benzyl-	HCl	88	74	*N-p*-Tolylphenylacet-	HCl	1·0	100	60
(18) 2-1'-Naphthyl-	Picrate	181·5	88	*N*-Phenyl-1-naphthyl-acet-	Picrate	1·35	130	5
3 : 4 : 5 : 6-*Tetrahydropyrimidines.*								
(19) 2-Phenyl-	T	122	91	*N*-Phenyl-*N*-methyl-benz-	T	1·0	55	60
(20) 2-(*p*-Methyl-sulphonyl-phenyl)-	T	187	96	*N*-Ethyl-*p*-methyl-sulphonylbenz-	T	1·0	100	60
2 : 7-*Diaza*cyclo*heptanes.*								
(21) 1-Benzyl-	Picrate	131	89	*N-p*-Tolylphenylacet-	T	1·0	100	60
(22) 1-(*p*-Methyl-sulphonyl-phenyl)-	Picrate	186	71	*N*-2-Pyridyl-*p*-methyl-sulphonylbenz-	Picrate	1·25	140	5
(23) 1-3'-Pyridyl-	Dipicrate *	177	86	*N*-Phenylnicotin-	B	1·25	100	30

* New compound. * B = Benzenesulphonate. T = Toluene-*p*-sulphonate.

Notes to Table I.

Except where otherwise indicated, the dihydroglyoxalines and ring homologues have been described in Part VI (*J.*, 1947, 497) and the known compounds were identified by comparison with authentic specimens.

(1), (2) Chitwood and Reid (*J. Amer. Chem. Soc.*, 1935, **57**, 2424) state that 2-methyl-4 : 5-dihydroglyoxalinium picrate has m. p. 205°. Aspinall (*ibid.*, 1939, **61**, 822) records m. p. 204°. See also Note (26) of Part IX (*J.*, 1948, 1521). (3) Chitwood and Reid (*loc. cit.*) and Aspinall (*loc. cit.*) state that the picrate has m. p. 137°. (5) The reaction mixture consisted of *N-cyclo*hexylphenylacetamidinium chloride (2·5 g.), ethylenediamine (1 c.c.), and nitrobenzene (5 c.c.). (6) *N*-Phenyl*cyclo*hexanecarboxyamidine (1·01 g.), 2-aminoethylammonium toluene-*p*-sulphonate (1·16 g.), and aniline (1 c.c.) gave 2-*cyclo*hexyl-4 : 5-*dihydroglyoxalinium toluene-p-sulphonate*, m. p. 171° (Found: N, 8·7. $C_{14}H_{20}O_3N_2S$ requires N, 8·6%). (8) 2-*Phenyl*-4 : 5-*dihydroglyoxalinium benzoate* consisted of rectangular plates, m. p. 115·5° (Found: N, 10·5. $C_{15}H_{14}O_2N_2$ requires N, 10·34%). (14) 2-*o*-*Chlorophenyl*-4 : 5-*dihydroglyoxalinium toluene-p-sulphonate* crystallised in colourless plates, m. p. 163° (Found: N, 8·0. $C_{16}H_{17}O_3N_2ClS$ requires N, 7·9%). (15) 2-(3 : 4-*Dimethoxyphenyl*)-4 : 5-*dihydro-*

Notes to Table I (contd.).

glyoxalinium benzenesulphonate had m. p. 192—192·5° (Found: N, 7·9. $C_{11}H_{16}O_3N_2S$ requires N, 7·7%). (16) 2-2′-*Naphthyl*-4 : 5-*dihydroglyoxalinium benzenesulphonate* separated from *iso*propanol in slender needles, m. p. 188·5° (Found: N 7·9. $C_{19}H_{18}O_3N_2S$ requires N, 7·9%). (19) The reaction mixture consisted of *N*-phenyl-*N*-methylbenzamidine (1·05 g.), trimethylenediamine (0·37 g.), ammonium toluene-*p*-sulphonate (0·95 g.), and dimethylaniline (0·53 c.c.). (20) The reaction mixture consisted of *N*-ethyl-*p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate (1·99 g.), trimethylenediamine (0·37 g.), and nitrobenzene (5 c.c.). (22) An aqueous solution of the reaction product from *N*-phenylnicotinamidine (0·4 g.), tetramethylenediamine (0·2 g.), and ammonium benzenesulphonate (0·35 g.) was made alkaline with 5*N*-sodium hydroxide, and the crude solid was purified by sublimation, giving 1-3′-*pyridyl*-2 : 7-*diazacycloheptene*, m. p. 102° (Found: N, 23·8. $C_{10}H_{12}N_2$ requires N, 24·0%). The *dipicrate* separated from methanol in long needles, m. p. 177° (Found: N, 20·0. $C_{22}H_{18}O_{14}N_8$ requires N, 19·9%).

TABLE II.

Preparation of 2-*substituted* 1-*alkyl*-4 : 5-*dihydroglyoxalines from cyanides and N-alkylethylenediamines.*

	Reaction, temp.	Reaction, time (hrs.).	Yield, %	Base. B. p. /mm.	Base. Formula.	Base. Found, N, %.	Base. Reqd., N, %.
(1) 2-*Benzyl*-1-*methyl*-4 : 5-*dihydroglyoxaline* [a]	190°	1½	92	107°/1	$C_{11}H_{14}N_2$	15·6	16·1
(2) 2-p-*Methoxybenzyl*-1-*methyl*-4 : 5-*dihydroglyoxaline*	190	1	69	—	—	—	—
(3) 2-1′-*Naphthylmethyl*-1-*methyl*-4 : 5-*dihydroglyoxaline* [b]	190	1	87	—	—	—	—
(4) 1 : 8-*Di*-(1-*methyl*-4 : 5-*dihydro*-2-*glyoxalinyl*)*octane*	190	2	53	—	—	—	—
(5) 2-*Benzyl*-1-*ethyl*-4 : 5-*dihydroglyoxaline*	190	3	83	109—112/ 1·5	$C_{12}H_{16}N_2$	14·9	14·9

[a] *Hydrochloride*, m. p. 88° (Found: N, 13·2. $C_{11}H_{15}N_2Cl$ requires N, 13·3%). [b] *Hydrochloride*, m. p. 241° (Found: N, 10·9. $C_{15}H_{17}N_2Cl$ requires N, 10·75%).

	Toluene-p-*sulphonate.* M. p.	Formula.	Found, N, %.	Reqd., N, %.	*Picrate.* M. p.	Formula.	Found, N, %.	Reqd., N, %.
(1)	—	—	—	—	125—125·5°	$C_{17}H_{17}O_7N_5$	17·4	17·4
(2)	114°	$C_{19}H_{24}O_4N_2S$	7·55	7·45	172·5	$C_{18}H_{19}O_7N_5$	16·4	16·2
(3)	—	—	—	—	181—181·5	$C_{21}H_{19}O_7N_5$	15·5	15·45
(4)	149·5—150·5	$C_{36}H_{44}O_6N_4S_2$	9·1	9·0	167	$C_{32}H_{32}O_{14}N_{10}$	19·2	19·0
(5)	—	—	—	—	141	$C_{18}H_{19}O_7N_5$	17·1	16·8

Notes to Table II.

The compounds described in the Table are new with the exception of 2-benzyl-1-methyl-4 : 5-dihydroglyoxaline which is mentioned, without physical constants, by Hartmann and Isler (*Arch. exp. Path.*, 1939, **192**, 141).

(1) The base gave erratic results on analysis by the Dumas method. (4) The preparation of this compound is described in detail below. (5) The base gave erratic results on analysis by the Dumas method. The hydrochloride was a gum but 2-*benzyl*-1-*ethyl*-4 : 5-*dihydroglyoxalinium sulphate* was obtained in deliquescent crystals, m. p. 151—152° (Found: N, 12·0. $C_{24}H_{34}O_4N_4S$ requires N, 11·8%).

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was crystallised from alcohol (50 c.c.) giving 25 g. of 2-*benzyl*-1 : 3-*dimethyl*-4 : 5-*dihydroglyoxalinium picrate*, m. p. 129°. This salt gave erratic results on Dumas analysis (Found: N, 17·4, 16·4, 17·4. $C_{17}H_{19}O_7N_5$ requires N, 16·8%). The picrate was treated with 5*N*-hydrochloric acid and, after removal of picric acid by extraction with benzene, the aqueous solution was evaporated to dryness and the residue crystallised from *iso*propanol giving large deliquescent octahedral crystals of the *chloride*, m. p. 210° (Found: N, 12·7. $C_{12}H_{17}N_2Cl$ requires N, 12·5%).

When 2-benzyl-4 : 5-dihydroglyoxaline (8 g.) was added to a stirred solution of methyl toluene-*p*-sulphonate (20 g., 2·15 mols.) in benzene (25 c.c.), the temperature rose to 33° in 15 minutes and then fell again, the solution remaining homogeneous. On addition of 5*N*-sodium hydroxide (20 c.c., 2 mols.) the temperature again rose to 30°. After being stirred for an hour, the product was neutralised (brilliant-yellow) with toluene-*p*-sulphonic acid, and the aqueous layer was separated and evaporated to dryness. The residue consisted of sodium toluene-*p*-sulphonate and an acetone-soluble gum (13 g.) which on treatment with 2*N*-lithium picrate afforded a solid *picrate*, m. p. 165·5—166°, probably the picrate of *N*-2-dimethylaminoethylphenylacetamide (Found: C, 50·0; H, 4·9; N, 16·0. $C_{18}H_{21}O_8N_5$ requires C, 49·7; H, 4·8; N, 16·1%).

The dimethotoluene-p-*sulphonate of* 1 : 2-*di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*ethane*. This separated as an oil when the dihydroglyoxaline (3·46 g.) and methyl toluene-*p*-sulphonate (3·72 g., 2 mols.) were boiled in benzene solution (20 c.c.). The quaternary *salt*, m. p. 167—169° (6·53 g., 91%), crystallised on trituration with acetone, and the m. p. remained unchanged after crystallisation from *iso*propanol (Found: N, 7·8. $C_{38}H_{46}O_6N_4S_2$ requires N, 7·8%). The corresponding *dimethopicrate*,

prepared by double decomposition, separated from ethanol in flat needles, m. p. 175° (Found: N, 17·0. $C_{34}H_{34}O_{14}N_{10}$ requires N, 16·8%).

Methosalts of 1 : 8-*di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*octane*. The oily base obtained from the dihydroglyoxalinium ditoluene-*p*-sulphonate (15·5 g.) and 2·5N-sodium hydroxide (50 c.c.) reacted exothermally with a solution of methyl toluene-*p*-sulphonate (10·2 g., 2·2 mols.) in benzene (10 c.c.), and the metho-salt separated as an oil which crystallised on manipulation. After recrystallisation from a mixture of methanol and acetone, the *dimethotoluene-p-sulphonate* (12 g., 74%) had m. p. 158—160° (Found: N, 8·7. $C_{36}H_{46}O_6N_4S_2$ requires N, 8·6%). The *dimethopicrate* separated from methanol in orange blades, m. p. 134° (Found: N, 18·2. $C_{36}H_{46}O_{14}N_{10}$ requires N, 18·3%).

2-p-*Hydroxy*- *and* 2-p-*Methoxy*-*benzyl*-4 : 5-*dihydroglyoxalines*. 2-*Benzylglyoxaline, and* 2-*Benzyl*-3 : 4 : 5 : 6-*tetrahydropyrimidine*.—*p*-Hydroxybenzyl cyanide (6·65 g.), prepared in 60% yield from *p*-aminobenzyl cyanide as described by Kessler and Hanke (*J. Biol. Chem.*, 1919, **39**, 585), and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g., 1 mol.) were heated at 155° for 1½ hours. The solid was crystallised from *iso*propanol (20 c.c.), giving unchanged 2-aminoethylammonium toluene-*p*-sulphonate (3 g.) and then 2-p-*hydroxybenzyl*-4 : 5-*dihydroglyoxalinium toluene*-p-*sulphonate* (11·0 g., 63%), m. p. 146—147°, unchanged after recrystallisation from water or alcohol (Found: N, 8·05. $C_{19}H_{22}O_4N_2S$ requires N, 8·0%). The *picrate* crystallised from water in rhombs, m. p. 161° (Found: N, 17·55. $C_{15}H_{13}O_8N_5$ requires N, 17·3%).

p-Methoxybenzyl cyanide (11·76 g.), b. p. 107—110°/1 mm., obtained in 91% yield by methylating the hydroxy-cyanide with methyl iodide and alcoholic sodium ethoxide, and 2-aminoethylammonium toluene-*p*-sulphonate (18·56 g., 1 mol.) afforded a solid when heated at 190° for 1 hour. After being triturated with acetone and recrystallised from *iso*propanol (60 c.c.) this solid afforded 2-p-*methoxybenzyl*-4 : 5-*dihydroglyoxalinium toluene*-p-*sulphonate* (20 g., 69%), m. p. 138° (Found: N, 7·8. $C_{19}H_{22}O_4N_2S$ requires N, 7·7%). The corresponding *picrate* had m. p. 119° (Found: N, 16·8. $C_{17}H_{17}O_9N_5$ requires N, 16·7%), and 2-p-*methoxybenzyl*-4 : 5-*dihydroglyoxaline* separated from benzene in flat needles, m. p. 121—122° (Found: N, 15·0. $C_{11}H_{14}ON_2$ requires N, 14·7%).

When 2-benzyl-4 : 5-dihydroglyoxaline (8 g.) was heated at 250° with a 40% cobalt–kieselguhr catalyst (1 g.) evolution of hydrogen was complete in 45 minutes. The product was separated from the catalyst by extraction with benzene, and was converted into the hydrochloride by shaking the benzene solution with 2N-hydrochloric acid (50 c.c.). The residue obtained by evaporating the aqueous solution was crystallised from *iso*propanol giving colourless, deliquescent needles of 2-*benzylglyoxalinium chloride* (7·0 g., 72%), m. p. 176° (Found: N, 14·2. $C_{10}H_{11}N_2Cl$ requires N, 14·4%). The picrate had m. p. 172° and the free base m. p. 125°; Sonn and Grief (*Ber.*, 1933, **66**, 1900) record 172° and 125—126°, respectively.

When benzyl cyanide (11·7 g.), trimethylenediammonium ditoluene-*p*-sulphonate (20·9 g.) and tetramethylenediamine (4·0 g.) were heated at 190° for an hour, and the base, liberated with 5N-sodium hydroxide (25 c.c.) and collected in benzene, was distilled, 2-*benzyl*-3 : 4 : 5 : 6-*tetrahydropyrimidine* (15·0 g., 86%) was obtained in colourless needles m. p. 114—114·5°, b. p. 135—136°/0·5 mm. (Found: N, 16·2. $C_{11}H_{14}N_2$ requires N, 16·1%). The *picrate* separated from methanol in prisms m. p. 174·5° (Found: N, 16·3, 16·9. $C_{17}H_{17}O_7N_5$ requires N, 17·4%). 2-*Benzyl*-3 : 4 : 5 : 6-*tetrahydropyrimidinium chloride*, prepared from the base and hydrogen chloride in acetone, had m. p. 210° (Found: N, 13·3. $C_{11}H_{15}N_2Cl$ requires N, 13·3%).

RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO., LTD., NOTTINGHAM.

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175. *Flavonols from the Bark of* Melicope ternata. *Part III. A Synthesis of Quercetin* 3 : 3′-*Dimethyl Ether, Quercetin* 3 : 7 : 3′-*Trimethyl Ether, Quercetin* 3 : 5 : 7 : 3′-*Tetramethyl Ether, Ternatin, and Related Benzyl Ethers.*

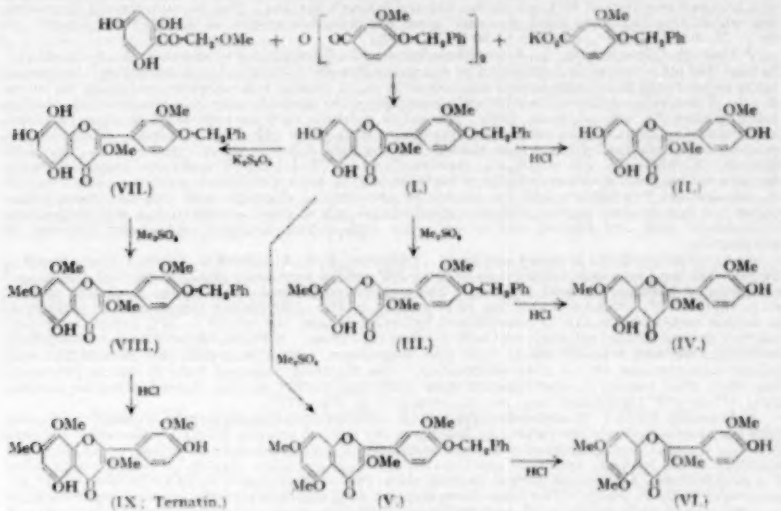
By LINDSAY H. BRIGGS and R. H. LOCKER.

The above compounds have been synthesised by combining Allan and Robinson's flavonol synthesis (*J.*, 1924, **125**, 2192) and Seshadri's recent methods of nuclear oxidation (*Proc. Indian Acad. Sci.*, 1948, **28**, *A*, 1).

By combining the above flavonol synthesis, protection of appropriate free phenolic groups by formation of their benzyl ethers, and the nuclear oxidation with potassium persulphate (see Seshadri, *loc. cit.*, for summary), the 3 : 3′-*dimethyl*, 3 : 7 : 3′-trimethyl, and 3 : 5 : 7 : 3′-*tetramethyl ethers* of quercitin, and also ternatin (5 : 4′-dihydroxy-3 : 7 : 8 : 3′-tetramethoxyflavone; cf. Part I, *J.*, 1949, 2157), have been synthesised according to the following scheme.

Condensation of *O*-benzylvanillic anhydride with ω-methoxyphloracetophenone in the presence of potassium *O*-benzylvanillate at 160—170° afforded 5 : 7-*dihydroxy*-4′-*benzyloxy*-3 : 3′-*dimethoxyflavone* (I), hydrolysed by hydrochloric acid–acetic acid to quercetin 3 : 3′-dimethyl ether (II). Partial methylation of (I) gave 5-*hydroxy*-4′-*benzyloxy*-3 : 7 : 3′-*trimethoxyflavone* (III), hydrolysed as before to quercetin 3 : 7 : 3′-trimethyl ether (IV), described by Kuhn

and Low (*Ber.*, 1944, **77**, 202). Complete methylation of (I) produced *4'-benzyloxy-3 : 5 : 7 : 3'-tetramethoxyflavone* (V), hydrolysed as previously to quercetin **3 : 5 : 7 : 3'**-tetramethyl ether. Nuclear oxidation of (I) with potassium persulphate (cf. Seshadri, *loc. cit.*, and Baker and Brown, *J.*, 1948, 2303 for the mechanism of the reaction) introduced a phenolic group at $C_{(8)}$, forming *5 : 7 : 8-trihydroxy-4'-benzyloxy-3 : 3'-dimethoxyflavone* (VII) in poor yield, which was partly methylated to *5-hydroxy-4'-benzyloxy-3 : 7 : 8 : 3'-tetramethoxyflavone* (VIII). Hydrolysis of the last compound, as before, afforded **5 : 4'**-dihydroxy-**3 : 7 : 8 : 3'**-tetramethoxyflavone (IX), identical in all respects with ternatin, the structure of which, suggested in Part I (*loc. cit.*), is thus confirmed.



Experimental.

(All m. p.s are corrected.)

Methyl O-Benzylvanillate.—Methyl vanillate, m. p. 62°, was prepared from vanillin *via* vanillic acid (Pearl, *J. Org. Chem.*, 1947, **12**, 86), esterification being by methyl alcohol and sulphuric acid (Matsmoto, *Ber.*, 1878, **11**, 128). Methyl vanillate (85 g., 1 mol.) and potassium hydroxide (27·5 g., 1 mol.) were dissolved separately in hot methyl alcohol (total, 125 c.c.). Benzyl chloride (60 g., 1 mol.) was added, and the mixture heated under reflux for 5 hours and filtered hot. The potassium chloride was washed with hot methyl alcohol, the combined filtrate concentrated and cooled, whereupon long colourless prisms (95·5 g.) separated, m. p. 86—86·5° (after recrystallisation from alcohol) (Found: C, 70·5; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). Alkaline hydrolysis afforded *O*-benzylvanillic acid, m. p. 173·5—175·5° (Lovecy, Robinson, and Sugasawa, *J.*, 1930, 821), converted into the anhydride, m. p. 137·5—193·5°, by treatment with thionyl chloride and pyridine (*idem, ibid.*). The potassium salt of *O*-benzylvanillate was formed by mixing equimolecular quantities of the acid and potassium hydroxide in hot alcohol, and concentration. The silky needles which formed were very soluble in alcohol and decomposed and carbonised above 250°.

5 : 7-Dihydroxy-4'-benzyloxy-3 : 3'-dimethoxyflavone.—*O*-Benzylvanillic anhydride (38 g., 2·5 mols.), potassium *O*-benzylvanillate (13·8 g., 1·5 mols.), and ω-methoxyphloracetophenone (6·1 g., 1 mol.; Slater and Stephen, *J.*, 1920, **117**, 312) were powdered together and heated at 160—170° for 2 hours. The powdered cake was dissolved in alcohol (300 c.c.) and water (20 c.c.) containing potassium hydroxide (20 g.), and the solution was boiled for 10 minutes before the alcohol was distilled off under reduced pressure almost to dryness. A yellow precipitate (7·7 g.) formed when carbon dioxide was passed into the solution of the yellow residue in water (300 c.c.). Pale yellow needles separated, having m. p. 258—259° when crystallised from acetone (Found: C, 68·2; H, 4·9. $C_{25}H_{22}O_7$ requires C, 68·6; H, 4·7%). The *flavone* is insoluble in sodium carbonate or concentrated hydrochloric acid but soluble in 10% sodium hydroxide solution or concentrated sulphuric acid with a yellow and an intense yellow colour, respectively. It gives a brown colour with alcoholic ferric chloride solution and a strong red colour when reduced with magnesium, hydrochloric acid, and alcohol and also with sodium amalgam and alcohol followed by acidification.

5 : 7 : 4′-*Trihydroxy*-3 : 3′-*dimethoxyflavone* (***Quercetin* 3 : 3′-*Dimethyl Ether***).—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (100 mg.) was heated on the water-bath with glacial acetic acid (4 c.c.) and concentrated hydrochloric acid (2 c.c.) for an hour. The flocculent yellow precipitate, obtained by pouring the mixture into water, was coagulated by heating on the water-bath for ½ hour and crystallised 3 times from alcohol, yielding yellow plates, m. p. 257—258° (Found : C, 61·8; H, 4·2. $C_{17}H_{14}O_7$ requires C, 61·8; H, 4·2%). The *flavone* is slightly soluble in sodium hydrogen carbonate solution, readily soluble in sodium carbonate and hydroxide solution with a bright yellow colour. It is insoluble in concentrated hydrochloric acid but soluble in concentrated sulphuric acid with an intense yellow colour. In a buffer at pH 9·8, a stable yellow colour is formed. A brown colour is given with alcoholic ferric chloride solution, and a strong red colour when reduced both with magnesium in concentrated hydrochloric acid and alcohol and with sodium amalgam and alcohol followed by acidification. The *triacetate* of the flavone was produced by dissolving 23 mg. in acetic anhydride (0·5 c.c.) and one drop of 60% perchloric acid and ½ hour's keeping. The product, formed by pouring into water, separated from ethyl or methyl alcohol in colourless needles, m. p. 199—200° (Found : C, 60·7; H, 4·5. $C_{23}H_{20}O_{11}$ requires C, 60·5; H, 4·4%).

5-Hydroxy-4′-benzyloxy-3 : 7 : 3′-*trimethoxyflavone*.—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (320 mg.) was partly methylated by dissolving it in dry acetone (18 c.c.) and heating the mixture under reflux for 6½ hours with methyl sulphate (0·08 c.c., 1·1 mols.) and anhydrous potassium carbonate (2 g.). The acetone solution, together with washings of the insoluble salts, was concentrated, yielding yellow prisms (68 mg.), m. p. *ca.* 154°. The yellow insoluble salts were dissolved in water, acidified, and warmed to coagulate the product, a light yellow solid, m. p. 153—154° (175 mg.). The combined product was crystallised 3 times from alcohol, forming light-yellow plates of constant m. p. 151—152° (Found : C, 68·8; H, 5·3. $C_{25}H_{24}O_7$ requires C, 69·1; H, 5·1%). The *flavone*, typical of many flavones with a free 5-hydroxy-position, is insoluble in 10% sodium hydroxide solution. It is insoluble in concentrated hydrochloric acid but soluble in concentrated sulphuric acid with an intense yellow colour. A brown colour is given with alcoholic ferric chloride solution, a scarlet colour with magnesium, hydrochloric acid, and alcohol, and a red colour with sodium amalgam and alcohol followed by acidification.

5 : 4′-*Dihydroxy*-3 : 7 : 3′-*trimethoxyflavone* (***Quercetin* 3 : 7 : 3′-*Trimethyl Ether***).—The preceding flavone (130 mg.) was hydrolysed for an hour at 100° with a mixture of glacial acetic acid (7 c.c.) and concentrated hydrochloric acid (3·5 c.c.). The product crystallised from alcohol in slender needles, m. p. 167—168·5°. Kuhn and Low (*loc. cit.*) record m. p. 169—170° for this compound. It is insoluble in sodium carbonate solution or concentrated hydrochloric acid, but soluble in 10% sodium hydroxide solution or concentrated sulphuric acid with a yellow coloration. A brown colour is given with alcoholic ferric chloride, and a scarlet colour both with magnesium, hydrochloric acid, and alcohol and with sodium amalgam and alcohol after acidification. The diacetate, prepared from 20 mg. as previously described, after successive crystallisation from ethyl and methyl alcohol, formed prismatic needles, m. p. 177·5—178° (Kuhn and Low, *loc. cit.*, record m. p. 174—175°).

4′-Benzyloxy-3 : 5 : 7 : 3′-*tetramethoxyflavone*.—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (200 mg.) was completely methylated by heating in dry acetone solution (15 c.c.) with methyl sulphate (0·3 c.c., 6 mols.) and anhydrous potassium carbonate (1 g.) for 3 hours. The acetone solution and washings of the insoluble salts were concentrated and gave colourless crystals (170 mg.), which, after 2 crystallisations from alcohol, formed needles, m. p. 162—163° (Found : C, 69·5; H, 5·5. $C_{19}H_{18}O_7$ requires C, 69·6; H, 5·4%). The *flavone* is insoluble in 10% sodium hydroxide solution, slightly soluble in concentrated hydrochloric acid, and freely soluble in concentrated sulphuric acid with weak and intensely yellow colours, respectively. There is no colour with alcoholic ferric chloride solution, but a scarlet colour with magnesium, hydrochloric acid, and alcohol as well as with sodium amalgam and alcohol followed by acidification.

4′-Hydroxy-3 : 5 : 7 : 3′-*tetramethoxyflavone* (*Quercetin* 3 : 5 : 7 : 3′-*Tetramethyl Ether*).—The preceding flavone (110 mg.) was hydrolysed with glacial acetic acid (4 c.c.) and concentrated hydrochloric acid (2 c.c.) for an hour at 100°. After addition of boiling water (50 c.c.) and cooling, pale yellow slender needles separated, which, after recrystallisation from alcohol, yielded light yellow prisms, m. p. 202—203° (Found : C, 63·5; H, 5·2. Calc. for $C_{19}H_{18}O_7$: C, 63·7; H, 5·0%). Rao and Seshadri (*J.*, 1947, 771) record very pale yellow, rectangular plates and prisms, m. p. 200—201°, for this compound. The flavone is insoluble in sodium hydrogen carbonate solution, soluble in sodium carbonate and sodium hydroxide solutions with bright yellow colours, and readily soluble in concentrated hydrochloric or sulphuric acid with an intense yellow colour. No colour is given with alcoholic ferric chloride solution, but a red colour when reduced both with magnesium, hydrochloric acid, and alcohol and with sodium amalgam and alcohol after acidification. The acetate, prepared as previously from 30 mg., after repeated crystallisation from alcohol, formed colourless needles, m. p. 179·5° (Found : C, 63·4; H, 5·1. Calc. for $C_{21}H_{20}O_8$: C, 63·0; H, 5·0%). Rao and Seshadri (*loc. cit.*) record m. p. 178—180°.

5 : 7 : 8-Trihydroxy-4′-benzyloxy-3 : 3′-*dimethoxyflavone*.—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (2·7 g., 1 mol.) was added to a solution of potassium hydroxide (2·7 g.) in water (450 c.c.). Complete dissolution did not occur owing to the limited solubility of this flavone in aqueous alkali. Potassium persulphate (3·5 g., 2 mols.), dissolved in water (100 c.c.), was added dropwise during 1 hour. It was found in a trial run that warming to complete dissolution after the addition of persulphate gave a better yield than did adding pyridine. The mixture was therefore heated to 53°, solution then being nearly complete, and set aside overnight. After removal of a yellow sediment (0·4 g.), the filtrate was acidified, filtered, and extracted with ether. The aqueous residue was then treated with sodium sulphite (6 g.) and concentrated hydrochloric acid (50 c.c.) on the water-bath for 1½ hours. A brown solid (0·4 g.) separated, which, after repeated crystallisation from alcohol (charcoal), formed deep yellow needles, m. p. 198—199° (Found : C, 66·0; H, 5·2. $C_{24}H_{20}O_8$ requires C, 66·1; H, 4·6%). No further product could be obtained from the residue by continuous extraction with ether. The *flavone* is insoluble in sodium carbonate solution but soluble in sodium hydroxide solution, giving a yellowish-brown colour which rapidly fades to a colourless solution with black insoluble particles, the solution finally changing

to a faint blue. In a buffer at pH 9·6 it gives a bright yellow solution which slowly fades. It is insoluble in concentrated hydrochloric acid but soluble in concentrated sulphuric acid with an intense yellow colour. A dark brown colour is given with alcoholic ferric chloride solution, and a reddish-brown colour on reduction with magnesium, hydrochloric acid, and alcohol. Only a weak yellow colour is produced by sodium amalgam and alcohol followed by acidification.

5-Hydroxy-4′-benzyloxy-3 : 7 : 8 : 3′-tetramethoxyflavone.—The preceding flavone (185 mg., 1 mol.), dissolved in dry acetone, was heated under reflux for 6 hours with methyl sulphate (0·09 c.c., 2·2 mols.) and anhydrous potassium carbonate. The acetone solution and washings of the insoluble salts were concentrated and acidified with one drop of concentrated hydrochloric acid. On cooling, yellow needles separated which, after recrystallisation from alcohol, had m. p. 170—171° (33 mg.) (Found: C, 67·1; H, 5·3. $C_{28}H_{28}O_8$ requires C, 67·2; H, 5·2%). The *flavone* is insoluble in 10% sodium hydroxide solution or concentrated hydrochloric acid, but soluble in concentrated sulphuric acid with an intense yellow colour. A green colour is given with alcoholic ferric chloride solution, and a strong pink colour with magnesium, hydrochloric acid, and alcohol; reduction with sodium amalgam and alcohol followed by acidification produces a violet colour.

5 : 4′-Dihydroxy-3 : 7 : 8 : 3′-tetramethoxyflavone (*Ternatin*).—The preceding flavone (25 mg.) was hydrolysed with glacial acetic acid (1 c.c.) and concentrated hydrochloric acid (0·5 c.c.) for one hour at 100°. On pouring the solution into boiling water (10 c.c.), pale yellow needles (18 mg.) separated on cooling, which, after recrystallisation from alcohol, had m. p. 210·5—212·5°, undepressed by a specimen of natural ternatin, m. p. 210—212°. The ultra-violet and visible spectra of the synthetic and the natural specimen were also identical (forthcoming communication). The synthetic product was also insoluble in sodium carbonate solution but soluble in sodium hydroxide solution, and gave a green colour with ferric chloride solution. The acetate, prepared as previously from 6 mg., on crystallisation from alcohol, formed colourless needles, m. p. 168—169°, which did not depress the m. p. of a sample prepared from natural sources. The synthetic acetate, like that from a natural sample, is photosensitive, becoming orange on exposure to light (Found, on a sample crystallised from both sources: C, 60·6; H, 4·8. Calc. for $C_{29}H_{30}O_{10}$: C, 60·3; H, 4·8%).

The analyses are by Drs. Weiler and Strauss, Oxford. We are indebted to the Chemical Society, the Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand, and the Research Grants Committee of the University of New Zealand for grants, and one of us (R. H. L.) for a Research Scholarship.

AUCKLAND UNIVERSITY COLLEGE,
AUCKLAND, NEW ZEALAND.

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176. *The Chemistry of the* Mitragyna *Genus. Part I.*

By G. M. BADGER, J. W. COOK, and P. A. ONGLEY.

The alkaloids of the leaves and bark of several species of *Mitragyna* have been examined as a preliminary to a more intensive chemical study of compounds of this class. Rotundifoline has been extracted from the leaves, and rhyncophylline from the bark, of *M. ciliata*. The identity of rhyncophylline with mitrinermine, suggested by Raymond-Hamet and supported by Barger *et al.* but disputed by Millat, has been established. A new phenolic alkaloid, *mitragynol*, has been isolated from *M. rotundifolia*; its methyl ether has been shown to be identical with dihydrorotundifoline. The hitherto unknown *dextro*-form of mitraphylline has been isolated from *M. rubrostipulacea*. Evidence has been obtained that the base, $C_9H_{13}N$, obtained by Barger *et al.* by selenium dehydrogenation of rotundifoline is 3 : 4-diethylpyridine.

Quinovic acid has been extracted from both leaves and bark of several species of *Mitragyna*, and a sterol from the bark of *M. inermis* has been identified as β-sitosterol.

THIS communication is concerned mainly with the isolation and characterisation of the alkaloids from several species of *Mitragyna*, preliminary to a structural study of this group of alkaloids. The genus *Mitragyna* occurs in the natural order Rubiaceæ, which has provided the cinchona alkaloids and also yohimbine. The isolation of several *Mitragyna* alkaloids has already been reported by other workers. These alkaloids include: mitragynine, probably $C_{23}H_{30}O_4N_2$; mitraphylline (rubradinine), $C_{21}H_{28}O_4N_2$; mitraspecine, $C_{23}H_{34}O_5N_2$ (?); mitraversine, $C_{22}H_{34}O_4N_2$ (?); rhyncophylline, $C_{22}H_{28}O_4N_2$; and rotundifoline, $C_{22}H_{34}O_5N_2$. Their structures have been very little investigated although it is known that only one of the two nitrogen atoms is basic and it has been suggested that the other is in an indole ring. Possibly a carboline system is present (cf. Ing and Raison, *J.*, 1939, 986). In some of these alkaloids two of the oxygen atoms have been shown to be present in a carbomethoxyl group and one in a methoxyl group, but the remaining oxygen atoms have not been characterised.

"Mitrinermine" was isolated from *M. inermis* O. Kuntze by Raymond-Hamet and Millat (*Compt. rend.*, 1934, **199**, 587) and also from *M. stipulosa* O. Kuntze by the same workers (*J. Pharm. Chim.*, 1934, **20**, 577). We have now isolated it from the bark of *M. ciliata* and have established its identity by melting-point comparisons of the free base, its chloroaurate, and its chloroplatinate. It was suggested by Raymond-Hamet (*Compt. rend.*, 1936, **203**, 1383)

that "mitrinermine" might be identical with rhyncophylline, which Kondo, Fukuda, and Tomita (*J. Pharm. Soc. Japan*, 1928, **48**, 321) had isolated from *Ourouparia rhyncophylla* (N. O. Rubiaceæ). This view was supported by toxicity experiments with samples of "mitrinermine" and rhyncophylline (Raymond-Hamet, *Compt. rend. Soc. Biol.*, 1938, **128**, 777) and was accepted by Barger, Dyer, and Sargent (*J. Org. Chem.*, 1939, **4**, 418) who isolated from the leaves of *M. rotundifolia* (Roxb.) O. Kuntze an alkaloid which was indistinguishable from authentic samples of "mitrinermine" and rhyncophylline, and also a new alkaloid, rotundifoline. The identity of "mitrinermine" and rhyncophylline was later challenged by Millat (*Ann. Pharm. franç.*, 1946, **4**, 27) on the ground of supposed differences in elementary composition, colour reactions with Fröhde's reagent, melting point, and specific rotation. The analytical figures of Akamatsu (*Nagasaki Igakkai Zasshi*, 1928, **6**, 333; cf. Millat, *loc. cit.*) do, in fact, suggest $C_{21}H_{24}O_4N_2$ as the formula for rhyncophylline, but those of Kondo (*loc. cit.*) are in agreement with $C_{22}H_{26}O_4N_2$, which is also the formula for "mitrinermine." Moreover, M. Raymond-Hamet has informed us that the colour normally given by rhyncophylline with Fröhde's reagent is due to an impurity. Also, the melting point of mitrinermine is not 203°, as cited by Millat, but 215—216° (Raymond-Hamet and Millat, *loc. cit.*; *Bull. Sci. Pharmacol.*, 1934, **41**, 533), which agrees with that of rhyncophylline. We have carried out mixed melting point determinations with mitrinermine isolated from *M. inermis* and the alkaloid isolated by Barger, Dyer, and Sargent (*loc. cit.*) from *M. rotundifolia* and regarded by them as rhyncophylline. There was no depression, and this applies also to the chloroaurates and chloroplatinates prepared from the alkaloid from each source. The figures for these were in good agreement with those cited by Kondo for the rhyncophylline derivatives. Finally, a careful comparison of the specific rotation of the alkaloid from each source, using light of different wave-lengths, failed to show any differences. It is noteworthy that the specific rotations of this and other *Mitragyna* alkaloids vary very greatly with concentration.

Barger *et al.* (*loc. cit.*) described some degradation experiments with rhyncophylline. We have now obtained evidence that its molecule contains one double bond. Its solution in chloroform decolorises bromine without liberation of hydrogen bromide although it gives no colour with tetranitromethane. Hydrogenation in acetic acid solution did not take place with a palladium catalyst, but with Adams's platinum catalyst there was absorption of one molecular proportion of hydrogen.

From the leaves of *M. rotundifolia* Barger *et al.* (*loc. cit.*) isolated, not only rhyncophylline, but also rotundifoline. We have simplified the separation of these two alkaloids and have also isolated rotundifoline from the leaves of *M. ciliata*, from the bark of which we have obtained rhyncophylline. Although it is unusual for two alkaloids to occur, one in the bark and the other in the leaves of the same species, this is by no means unknown. The co-existence of the two alkaloids in both *M. ciliata* and *M. rotundifolia* suggests a close chemical relationship and it may be that rotundifoline is an oxidation product of rhyncophylline.

By the selenium dehydrogenation of rotundifoline Barger *et al.* (*loc. cit.*) obtained a mixture of bases from which they isolated a picrate, m. p. 134—135°, of composition indicating a base $C_9H_{13}N$. Witkop (*J. Amer. Chem. Soc.*, 1948, **70**, 3713) has shown that this base is not 2 : 4-dimethyl-3-ethylpyridine, the picrate of which has a similar melting point. Koenigs and Bernhart (*Ber.*, 1905, **38**, 3049) give m. p. 139° for the picrate of 3 : 4-diethylpyridine, which has the same composition, and we undertook some preliminary experiments on the synthesis of this base. Recently Karrer and Enslin (*Helv. Chim. Acta*, 1949, **32**, 1390) have described the formation of 3 : 4-diethylpyridine by degradation of corynanthyrine, which is itself formed by selenium dehydrogenation of the alkaloid corynantheine. We were fortunate enough to obtain a sample of Barger's picrate, given to us by Dr. Klyne, and found that its melting point was not depressed by admixture with synthetic 3 : 4-diethylpyridine picrate for a sample of which we are indebted to Professor Karrer. It would seem, therefore, that 3 : 4-diethylpyridine is a product of selenium dehydrogenation of rotundifoline.

With bromine in chloroform solution and with palladium and platinum catalysts in acetic acid, rotundifoline behaved exactly like rhyncophylline. *Dihydrorotundifoline*, obtained by hydrogenation with Adams's platinum catalyst, was isolated and characterised, and *rotundifoline dibromide* was also prepared. Rotundifoline gave a deep yellow colour with tetranitromethane, and also gave colours with Mandelin's and Erdmann's reagents but not with Fröhde's reagent. The similarity of the rotations of rotundifoline and dihydrorotundifoline suggests that the ethylenic bond in the former is unconjugated and this was confirmed by comparison of the absorption spectra, for which we are indebted to Dr. E. Clar who found that the two compounds gave almost identical spectra.

Through the good offices of Dr. W. Klyne, and the kindness of Drs. Dyer and Sargent, we have been able to examine some of the crude phenolic alkaloid extracted by Barger, Dyer, and Sargent (*loc. cit.*) from the leaves of *M. rotundifolia*. This was purified by chromatography on alumina and yielded a new crystalline alkaloid, *mitragynol*, $C_{21}H_{24}O_5N_2$, characterised as its *hydrochloride*. The colour reactions of mitragynol with Erdmann's, Fröhde's, and Mandelin's reagents were similar to those of rhyncophylline and rotundifoline, and ferric chloride in ether gave a red colour. Tetranitromethane gave an orange colour with mitragynol, but there was no other evidence of unsaturation; the compound did not decolorise bromine in chloroform, nor did it absorb hydrogen over Adams's platinum catalyst in acetic acid. Mitragynol appeared to have the character of a phenol, for it was soluble in sodium hydroxide solution, but not in sodium hydrogen carbonate solution, and gave a reddish-brown colour with ethanolic ferric chloride. By treatment with diazomethane mitragynol was converted into methylmitragynol which was insoluble in alkali and gave very little intensification of colour with ethanolic ferric chloride. Methylmitragynol proved to be identical with dihydrorotundifoline.

Differentiation between rotundifoline and dihydrorotundifoline was not easy, as the two compounds had almost the same melting point and there was no depression on mixing them. This applied also to the chloroplatinates and we did not succeed in preparing other crystalline salts. However, Barger's specimen of rotundifoline, isolated from *M. rotundifolia*, absorbed hydrogen equivalent to one double bond and also gave a very dark red colour with ferric chloride in ether. These characteristics were likewise shown by the rotundifoline which we isolated from *M. ciliata*, but not by dihydrorotundifoline or methylmitragynol, which we regard as identical. Moreover, by treatment of the last two substances with bromine under conditions which led to the formation of a dibromide from rotundifoline, brominated products could not be isolated. Rotundifoline gave a permanent flocculent precipitate with antimony pentachloride in chloroform; dihydrorotundifoline and methylmitragynol gave only a temporary haziness with this reagent.

Methoxyl determinations on these compounds gave results for which an explanation cannot yet be given. The determinations were carried out by Pregl's micro-modification of the Zeisel method. Mitragynol gave a value indicating the presence of two methoxyl groups; methylmitragynol, which is apparently obtained by methylation of a phenolic or enolic hydroxyl group also gave a value corresponding with two methoxyl groups. This latter value accords with that quoted by Barger *et al.* (*loc. cit.*), which we have confirmed, for rotundifoline. These authors found no *N*-methyl in rotundifoline. It appears, therefore, that the action of diazomethane on mitragynol methylates an acidic hydroxyl group to give a methoxyl group which is not hydrolysed under the conditions of the Zeisel determination. An example of failure of a methoxy-compound to respond to this analytical treatment had already been encountered by Dr. R. Schoental in these laboratories, and her results are recorded in an appendix to this communication. In her case lack of solubility may be the explanation, but this cannot apply in the cases of rotundifoline and methylmitragynol (dihydrorotundifoline).*

Mitraphylline has been isolated from *M. rubrostipulacea* (*Adina rubrostipulata* K. Schumann) by Michiels (Michiels and Leroux, *Bull. Acad. roy. med. Belg.*, 1925, **5**, 403; Michiels, *J. Pharm. Belg.*, 1935, **17**, 1049), by Denis (*Bull. Acad. roy. Belg.*, 1937, **23**, 174) who named it rubradinine, and by Raymond-Hamet (*Bull. Sci. pharmacol.*, 1939, **46**, 327); Michiels (*J. Pharm. Belg.*, 1931, **13**, 719) also isolated it from *M. stipulosa* (*M. macrophylla*). We have examined several samples of *M. rubrostipulacea* and have isolated *lævo*-mitraphylline from the leaves and *dextro*-mitraphylline from the bark. Michiels (*J. Pharm. Belg.*, 1931, **13**, 719) has reported "inactive" mitraphylline, and we also have isolated material which showed no optical rotation. Mitraphylline gave a yellow colour with tetranitromethane and formed a *dibromide*. It absorbed one molecule of hydrogen when treated in acetic acid with hydrogen and a palladium catalyst. With Adams's platinum catalyst one molecular proportion of hydrogen was rapidly absorbed, and two further molecular proportions were slowly taken up.

During extractions of the alkaloids from various species of *Mitragyna* we have observed the presence of a triterpene acid in considerable amount. This acid was isolated from the bark of *M. inermis* and from both bark and leaves of *M. ciliata* and *M. rubrostipulacea*. In every case it has been identified as quinovic acid, long known as a constituent of cinchona bark (natural order Rubiaceæ) (Liebermann, *Ber.*, 1884, **17**, 868) and more recently found in *Zygophyllum coccineum* L., an Egyptian plant of the natural order Zygophyllaceæ (Soliman, *J.*, 1939, 1760).

We have also examined a sample of sterol kindly given to us by M. Raymond-Hamet, who

* See also Nunn and Rapson, *J.*, 1949, 3155.

isolated it from the bark of *M. inermis*. After purification, determinations of the melting points and specific rotations of the sterol, its acetate, and its 3:5-dinitrobenzoate indicated that the sterol was β-sitosterol (cf. Ichiba, *Inst. Phys. Chem. Res., Tokyo*, **1935**, **28**, 112; Simpson and Williams, *J.*, **1937**, 733), and this view was supported by direct comparison with authentic specimens of β-sitosterol and its corresponding derivatives (Cook and Paige, *J.*, **1944**, 336).

Experimental.

Rhyncophylline.—A mixture of finely ground *M. inermis* bark (15 kg.) and calcium oxide (5 kg.) was moistened, air-dried at 40°, and then extracted with hot chloroform in a continuous extractor until a sample of extract no longer gave a precipitate with Mayer's reagent. After removal of the chloroform the residual paste was extracted with 3% hydrochloric acid until the residue was free from basic material. The alkaloid (2 g.) was then precipitated by addition of concentrated ammonia solution. Rhyncophylline then crystallised from methanol in small colourless prisms, m. p. 212—213°, not depressed by admixture with specimens supplied by Dr. Klyne, extracted from both *M. inermis* and *M. rotundifolia*. The chloroplatinate formed orange prisms (from methanol) which decomposed at 236° (Kondo *et al.*, *loc. cit.*, give 238° for the decomposition point of the chloroplatinate of rhyncophylline). The chloroaurate melted at 132° and then decomposed at 155° (Kondo gives 134° and 155°, respectively).

Similar extraction of the bark (500 g.) of *M. ciliata* gave crystalline rhyncophylline (0·1 g.), m. p. 211°; its chloroplatinate decomposed at 236—237°, and its chloroaurate at 155—157°, after melting at 133°. Mixed m. p. determinations showed no depressions.

A specimen of rhyncophylline extracted from *M. rotundifolia* by Barger, Dyer, and Sargent (*loc. cit.*) gave a chloroplatinate which formed orange prisms and decomposed at 235° after darkening (Found: C, 44·6; H, 5·0; Pt, 16·2. Calc. for $C_{44}H_{58}O_4N_4Cl_6Pt$: C, 44·8; H, 5·0; Pt, 16·55%), and a chloroaurate which melted at 132° and then decomposed at 155°. These values also showed no depressions when the specimens were mixed with corresponding compounds of rhyncophylline prepared from *M. inermis*.

Optical Rotations.—The following measurements, made with chloroform solutions at 19° ($l = 1$) serve to confirm the identity of the alkaloid (*I*) from *M. inermis* with that (*R*) isolated by Barger *et al.* (*loc. cit.*) from *M. rotundifolia*:

Sample.	Concn.	Wave-length of source:	[α]. 7000.	6500.	5900.	5500.	5000.
R	5·30		—	—	−6·0°	—	—
R	2·35		—	−12·6°	−14·3	−15·3°	−16·6°
I	2·26		−12·6°	−14·0	−15·7	−17·5	−18·7
R	1·00		−16·0	−18·0	−22·0	−28·0	−36·0
I	1·13		−17·7	−20·4	−23·0	−28·3	−37·2

Rotations were also measured of solutions in 2*N*-hydrochloric acid at 19° ($l = 1$) as follows (concentrations given as weight of base in 100 c.c. of acid):

	Concn.	7000.	6500.	5900.	5500.	5250.	5000.
R	1·50	+1·0°	+1·7°	+3·3°	+4·7°	+6·7°	+8·3°
I	1·50	+1·0	+1·7	+2·7	+4·0	+6·0	+8·0

Specific rotations given in the literature for rhyncophylline are $[\alpha]_D^{18}$ −14·7° (Kondo *et al.*) and $[\alpha]_D^{15}$ −14·5° (*c*, 2·5 in chloroform) (Barger *et al.*). For "mitrinermine," Raymond-Hamet and Millat (*J. Pharm. Chim.*, **1934**, **20**, 577) give [α] −23·0° (*c*, 1·45), −23·1° (*c*, 1·51), −26·4° (*c*, 1·45), and −26·5° (*c*, 1·19) (all in chloroform).

Rotundifoline.—A mixture of the minced leaves of *M. ciliata* (500 g.) and calcium oxide (100 g.) was moistened, dried, and extracted for 16 hours with hot chloroform. The extracted alkaloid was crystallised from ethanol (yield, 0·8 g.) and had m. p. 233°, not depressed on admixture with an authentic specimen of the rotundifoline of Barger *et al.* (*loc. cit.*), who give m. p. 233—234°. The observation that rotundifoline is sparingly soluble in chlorobenzene whereas rhyncophylline is easily soluble made it possible to effect a ready separation of these two alkaloids from the crude mixture obtained from *M. rotundifolia*. Polarimetric comparison (in chloroform at 21°; $l = 1$) of the alkaloid from *M. ciliata* (*C*) with Barger's rotundifoline (*Ro*) confirmed their identity.

	Concn.	7000.	6500.	5900.	5500.	5250.	5000.	4750.
C	2·10	+85·7°	+98·6°	+123·5°	+145·2°	+163·9°	+184·8°	+217·6°
Ro	2·10	+84·8	+97·6	+122·4	+143·8	+162·4	+184·3	+214·3

[Barger *et al.* (*loc. cit.*) give $[\alpha]_D^{15}$ + 124° (*c*, 2·14 in chloroform)].

The following rotations were observed for solutions of rotundifoline in 2*N*-hydrochloric acid at 21° (*c*, 2·48 g. per 100 c.c.; $l = 1$):

7000.	6500.	5900.	5500.	5250.	5000.	4750.
+44·8°	+48·4°	+60·9°	+70·6°	+79·0°	+90·7°	+109·6°

With Mandelin's reagent rotundifoline gave a brown colour which became olive-green on storage; with Fröhde's reagent there was no colour, and with Erdmann's reagent no immediate colour but a light brown colour developed on storage. A methoxyl determination was carried out on the sample of Barger's rotundifoline supplied by Dr. Klyne (Found: OMe, 16·2. Calc. for $C_{38}H_{44}O_5N_2$: 2OMe, 15·6%). The

chloroplatinate of rotundifoline had m. p. 232—234° (decomp.) (Found: C, 43·4; H, 5·1. $C_{22}H_{34}O_{10}N_2Cl_4Pt$ requires C, 43·7; H, 4·6%).

Rotundifoline was not hydrogenated in ethanolic solution with Adams's platinum catalyst or with Raney nickel at 75°/30 atmospheres. Attempted micro-hydrogenation in acetic acid with palladium-black was likewise unsuccessful, but with Adams's platinum catalyst in acetic acid one molecular proportion of hydrogen was absorbed. Repetition on a macro-scale led to the isolation of *dihydrorotundifoline*, which formed colourless needles (from methanol), m. p. 233°, not depressed on admixture with rotundifoline (Found: C, 65·6; H, 7·3. $C_{22}H_{34}O_4N_2$ requires C, 66·0; H, 7·1%). The rotation of dihydrorotundifoline in chloroform at 21° (*c*, 2·41) was as follows:

7000.	6500.	5900.	5500.	5250.	5000.	4750.
+96·7°	+103·7°	+123·7°	+147·7°	+163·5°	+189·6°	+220·3°

The chloroplatinate of dihydrorotundifoline had m. p. 224—226° (from methanol), not depressed on admixture with the chloroplatinate of methylmitragynol described below.

Rotundifoline was treated with bromine in chloroform at room temperature until no more was taken up, and the product was heated under reflux with acetone to reduce perbromide. The resulting *dibromide* was further purified by repeated dissolution in dilute hydrochloric acid and reprecipitation with aqueous ammonia. It formed an amorphous powder, m. p. 215° (Found: C, 47·2; H, 4·8; Br, 28·8. $C_{22}H_{34}O_4N_2Br_2$ requires C, 47·3; H, 4·7; Br, 28·6%).

3 : 4-*Diethylpyridine Picrate*.—A sample of the picrate of the base formed by selenium dehydrogenation of rotundifoline (Barger, Dyer, and Sargent, *loc. cit.*), given to us by Dr. Klyne, had micro-m. p. 131—133°. Its m. p. was not depressed when the salt was mixed with a specimen of 3 : 4-diethylpyridine picrate (micro-m. p., 134—136°) presented by Professor Karrer.

Mitragynol.—The pale brown amorphous phenolic alkaloid (10 g.) from *M. rotundifolia* (Barger *et al.*, *loc. cit.*), for which we are indebted to Dr. Klyne, was dissolved in chloroform (100 c.c.), and its solution passed through a column of alumina (2 × 12 cm.), previously saturated with benzene. The column was eluted with chloroform (150 c.c.). Evaporation of the solvent gave an amorphous mass which crystallised on storage with methanol (yield of colourless crystals, 5·8 g.). *Mitragynol* crystallised from methanol in colourless transparent needles which became opaque on storage. After being dried in a vacuum, it had m. p. *ca.* 130°, depending on the rate of heating (Found: C, 65·3; H, 6·9; N, 7·1; OMe, 15·45, 14·8. $C_{21}H_{32}O_4N_2$ requires C, 65·25; H, 6·8; N, 7·25; 2OMe, 16·0%). Specific rotations at different concentrations and wave-lengths were:

Concn.	7000.	6500.	5900.	5500.	5250.	5000.	4750.
4·24	+2·8°	+1·4°	+0·5°	−0·5°	−0·7°	−2·1°	
2·12	−2·8	−3·8	−4·7	−5·2	−6·6	−8·0	
1·06	−5·7	−7·6	−8·7	−10·4	−12·3	−13·2	

The *hydrochloride*, prepared in aqueous solution and recrystallised from water, formed colourless needles, m. p. 212—216° (Found: C, 59·6; H, 6·2; N, 6·8. $C_{21}H_{31}O_4N_2Cl$ requires C, 59·6; H, 6·4; N, 6·6%). The analytical specimen was dried at 100° *in vacuo*. Specific rotations in aqueous solution at 21° (*c*, 3·75; *l* = 1) were:

7000.	6500.	5900.	5500.	5250.	5000.	4750.
−30·9°	−34·9°	−42·9°	−51·4°	−57·1°	−64·3°	−71·4°

With Mandelin's reagent mitragynol gave a transient brown colour, changing to olive-green; with Fröhde's reagent there was no colour and with Erdmann's reagent a very faint brown colour on storage. Tetranitromethane gave an orange colour. Mitragynol gave no sparingly soluble chloroplatinate and did not absorb hydrogen in acetic acid over Adams's platinum catalyst.

For methylation, a solution of mitragynol (0·6 g.) in ether and methanol was set aside overnight with excess of ethereal diazomethane. The residue obtained by evaporation was recrystallised from methanol, giving colourless needles (0·46 g.), m. p. 232—233°, not depressed on admixture with dihydrorotundifoline (above) (Found: C, 65·8; H, 6·9; OMe, 15·4. Calc. for $C_{22}H_{34}O_4N_2$: C, 66·0; H, 7·1; OMe, 15·6%). Identity was confirmed by preparation of the *chloroplatinate*, which crystallised from ethanol in orange-yellow prisms, m. p. 224—226° (Found: C, 43·6; H, 5·1; Pt, 15·7. $C_{44}H_{68}O_{10}N_4Cl_4Pt$ requires C, 43·6; H, 4·8; Pt, 16·1%). The following rotations (in chloroform at 21°; *l* = 1) were observed with the dihydrorotundifoline (methylmitragynol) prepared in this way:

Concn.	7000.	6500.	5900.	5500.	5250.	5000.	4750.
3·28	+86·6°	+102·1°	+122·6°	+144·5°	+163·4°	+186·9°	+218·3°
1·64	+92·7	+109·7	+126·3	+151·2	+166·9	+194·5	+223·8
0·822	+88·0	+109·7	+128·0	+154·9	+178·0	+202·4	+225·5

Mitraphylline.—(*a*) Finely ground bark of *M. rubrostipulacea* (500 g.) was mixed with calcium oxide (125 g.), moistened, air-dried, and extracted for 16 hours with hot chloroform. The mitraphylline recovered from the extract formed long colourless needles, m. p. 262° (from methanol), and gave a picrate, m. p. 165° (Raymond-Hamet and Millat, *Bull. Sci. Pharmacol.*, 1935, **42**, 602, give m. p. varying between 258° and 267° for the alkaloid, and Denis, *loc. cit.*, gives m. p. 166° for the picrate). Specific rotations of the base in chloroform at 21° (*l* = 2) were:

Concn.	7000.	6500.	5900.	5500.	5250.	5000.	4750
1·96	+4·3°	+5·4°	+7·1°	+9·2°	+11·7°	+14·8°	+19·1°
0·98	+2·5	+3·5	+4·6	+5·6	+7·7	+10·2	+13·3

In 2*N*-hydrochloric acid at 21° ($l = 1$; concentrations in g. of base per 100 c.c.) the rotations were:

Concn.	7000.	6500.	5900.	5500.	5250.	5000.	4750.
2·70	+18·6°	+22·6°	+26·7°	+30·4°	+34·1°	+37·8°	+41·9°
1·35	+14·8	+17·8	+21·5	+28·9	+32·6	+36·3	+40·8

(*b*) Finely ground leaves of *M. rubrostipulacea* (500 g.), extracted similarly, gave the same alkaloid (2·8 g.), m. p. 261° alone or mixed with the sample described in the previous paragraph or with mitraphylline kindly given us by M. Raymond-Hamet. The picrate had m. p. 165°, not depressed by the picrate of the alkaloid from the bark. A sample of leaves supplied about 6 months later gave only one-tenth of the amount of alkaloid for the same weight of leaves; this was lævorotatory, having $[\alpha]_D^{20}$ −7·4° (*c*, 1·20 in chloroform) (Found: C, 68·3; H, 7·0; N, 7·3; OMe, 8·5. Calc. for $C_{21}H_{24}O_4N_2$: C, 68·0; H, 7·0; N, 7·6; OMe, 8·4%). For mitraphylline in chloroform, Raymond-Hamet and Millat (*loc. cit.*) give $[\alpha]_D$ −7·7° (*c*, 3·9) and −5·8° (*c*, 1·2), Raymond-Hamet (*Bull. Sci. Pharmacol.*, 1939, **46**, 327) gives $[\alpha]_D^{15}$ −9·8° (*c*, 0·51) and Denis (*loc. cit.*) gives $[\alpha]_D$ −22·27° (*c*, 4·8), whereas Michiels and Delvaux (*J. Pharm. Belg.*, 1931, **13**, 719) describes mitraphylline as having zero rotation. More recently we also have extracted the alkaloid from about a hundredweight of bark and leaves of *M. rubrostipulacea* and have isolated optically inactive mitraphylline.

Microhydrogenation of mitraphylline in acetic acid over Adams's platinum catalyst led to absorption of **3** moles of hydrogen. The first molecule was taken up in **18** minutes, and the other two each required **40** minutes. Microhydrogenation over palladium-black led to absorption of one mole of hydrogen.

Treatment of mitraphylline with bromine in chloroform at room temperature gave an amorphous product which was heated under reflux with acetone to decompose perbromide and then purified by repeated solution in dilute hydrochloric acid and reprecipitation with aqueous ammonia. The dibromide, an amorphous powder, m. p. 195—198°, was converted into its *chloroplatinate* which formed small yellow leaflets (from methanol) and decomposed at 190° (Found: C, 34·4; H, 3·95; Pt, 12·5. $C_{21}H_{24}O_4N_2Cl_2Br_2Pt$ requires C, 34·3; H, 3·7; Pt, 13·3%).

Quinovic Acid.—The *M. inermis* bark from which the alkaloid had been extracted (above) was kept for 24 hours in 10% sodium carbonate solution (20 galls.), and then percolated with a further equal volume. The bark was pressed manually, and the combined extracts were treated with "Supercel" and then acidified with 15% hydrochloric acid. The filtered precipitate was re-dissolved in alkali and reprecipitated after filtration from the "Supercel." The crude acid was purified by repeated crystallisation from ethanol, with charcoal. The yield of almost pure acid was 50 g.

The pure acid formed colourless crystals (Found: C, 73·8, 74·1; H, 9·3, 9·4%; equiv., by titration, 240, 248, 249. Calc. for $C_{30}H_{44}O_3$: C, 74·9; H, 9·5%; equiv., 243), m. p. 298° (alone or mixed with an authentic specimen of quinovic acid kindly presented by Professor L. Ruzicka), $[\alpha]_D^{20}$ +99° (*c*, 2·48 in pyridine). For the potassium salt (concn. expressed as g. of acid in potassium carbonate solution), $[\alpha]_D$ = +89° (*c*, 0·98) (lit.: m. p. of quinovic acid, 298°; $[\alpha]_D^{20}$ of potassium salt, +87°).

The methyl ester, prepared with excess of ethereal diazomethane, formed colourless crystals (from light petroleum), m. p. 172—173°, not depressed in admixture with an authentic specimen of methyl quinovate. It had $[\alpha]_D^{20}$ +117·4° (*c*, 2·12 in chloroform) (lit.: m. p. 173—174°; $[\alpha]_D^{20}$ +115·2°, +116·8°, in chloroform).

The acetyl derivative, prepared by heating the acid with excess of acetic anhydride under reflux, crystallised from methanol in colourless needles, m. p. 281—282° (lit., 284°) (Found: C, 73·0, 72·8; H, 9·05, 9·2. Calc. for $C_{32}H_{46}O_4$: C, 72·6; H, 9·15%).

Quinovic acid was also isolated from both bark and leaves of *M. ciliata* and *M. rubrostipulacea*. The following constants were given by the various specimens, and in all cases mixed m. p.s with authentic samples were carried out. The specific rotations are for the potassium salt, in water.

Source:	*M. inermis* bark.	*M. ciliata* bark.	*M. ciliata* leaves.	*M. rubrostipulacea* bark.	*M. rubrostipulacea* leaves.
M. p. of acid	298°	300°	298°	303°	301°
$[\alpha]_D^{20}$	+86	+87	+87	+43, +44	+86
M. p. of acetyl derivative	281—282°	280—281°	283°	284°	281—281·5°
M. p. of methyl ester	172—173°	172—173°	171—173°	171—173°	172—174°

β-Sitosterol from M. inermis.—A sample of a sterol obtained from benzene extracts of *M. inermis* bark, after removal of rhyncophylline, was presented to us by M. Raymond-Hamet. Repeated recrystallisation from methanol gave crystals of m. p. 134—135° and $[\alpha]_D^{20}$ −35·6° (*c*, 1·54 in chloroform). This sterol, which was unsaturated, was converted into its acetate by acetic anhydride in pyridine at room temperature, and into its **3**:5-dinitrobenzoate by **3**:5-dinitrobenzoyl chloride in boiling pyridine. The m. p.s of the sterol and its two derivatives were not depressed on admixture with *β*-sitosterol and the corresponding derivatives, isolated by Cook and Paige (*loc. cit.*) from *Calycanthus floridus*, and the satisfactory agreement between constants, given in the following table, confirms the identification of the sterol from *M. inermis* as *β*-sitosterol.

	Sterol from *M. inermis*.	*β*-Sitosterol.
M. p. of sterol	134—135°	137·5—138·5° [1]
$[\alpha]_D$ of sterol	−35·6	−34·0 [1]
M. p. of acetate	128°	126·5—127·5° [1]
$[\alpha]_D$ of acetate	−38·5 [2]	−34·7 [3]
M. p. of **3**:5-dinitrobenzoate	203—204°	208—209° [1]
$[\alpha]_D$ of **3**:5-dinitrobenzoate	−20·7 [4]	−21·7 [3]

[1] Cook and Paige's values (*loc. cit.*), *q.v.* for figures given by earlier workers. [2] *c*, 1·20 in chloroform at 21°. [3] Simpson and Williams, *J.*, 1937, 733. [4] *c*, 1·20 in chloroform at 20°.

This work was carried out during the tenure of an I.C.I. Research Fellowship by G. M. B. and of a Coats Fellowship by P. A. O., for both of which we express our indebtedness. The investigation has been made possible by the greatly appreciated co-operation of Sir John Simonsen, F.R.S., Director of the Colonial Products Research Council, and of the Chief Conservator of Forests, Nigeria, who arranged for the supply of African botanical material. We also express our gratitude to Messrs. Duncan Flockhart for carrying out bulk extractions, and to the following for gifts of compounds: Drs. W. Klyne, E. Dyer, and L. J. Sargent (for rotundifoline, rhyncophylline, crude mitragynol, and the picrate of a base formed by dehydrogenation of rotundifoline); M. Raymond-Hamet (for mitraphylline, rhyncophylline, and the sterol from *M. inermis*); Professor L. Ruzicka (for quinovic acid and its derivatives); Professor P. Karrer (for **3**: 4-diethylpyridine picrate). Microanalyses were carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

Appendix. By Miss R. Schoental.

In connection with a study of the metabolic oxidation products of some polycyclic aromatic hydrocarbons, specimens have been prepared of the dimethyl ethers of the anthraquinols formed by alkaline reduction of three anthraquinone derivatives. Unexpected difficulty was encountered in the analysis of **9**: 10-dimethoxy-**1**: **2**: **5**: 6-dibenzanthracene. Three attempts (by Mr. J. M. L. Cameron) to estimate the methoxyl content by Pregl's micro-modification of the Zeisel method gave a zero value, although the compound should contain two methoxyl groups. There can be little doubt that the structure is correctly assigned, for it is supported by the method of preparation and the elementary analysis of the compound and its picrate; moreover, the ultra-violet absorption spectrum of the dimethoxy-compound resembles very closely that of **1**: **2**: **5**: 6-dibenzanthracene (Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 320), with a shift towards the region of longer wave-length, which amounted to 100 A. for the longest band. This failure to hydrolyse the dimethyl ether is possibly caused by steric hindrance, but the compound is very sparingly soluble and this may be a contributory factor. Two other compounds of similar structure gave somewhat low values for the methoxyl content, which however clearly indicated the presence of two methoxyl groups in each case.

For preparation of these dimethoxy-compounds, the appropriate quinone was heated with zinc dust, aqueous sodium hydroxide, and methyl sulphate, the alkali and methyl sulphate being added alternately in small portions until the alkaline solution was almost completely decolorised. The product was extracted with benzene and the strongly fluorescent benzene solution was purified by chromatography on alumina. The concentrated benzene eluates were treated with light petroleum.

9: 10-*Dimethoxy*-**1**: **2**-*benzanthracene* formed colourless rhombic plates, m. p. 137—138° (Found: C, 83·35; H, 5·7; OMe, 19·3. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·6; OMe, 21·5%) (cf. Berenblum and Schoental, *Cancer Res.*, 1943, **3**, 686). **9**: 10-Dimethoxy-**1**: **2**: **7**: **8**-dibenzanthracene could not be obtained crystalline, but formed a *s-trinitrobenzene* complex which crystallised from ethanol in orange-yellow needles, m. p. 157—158° (Found: C, 65·35; H, 3·85; N, 7·7; OMe, 9·9. $C_{26}H_{21}O_8N_3$ requires C, 65·3; H, 3·8; N, 7·6; OMe, 11·2%). **9**: 10-*Dimethoxy*-**1**: **2**: **5**: **6**-*dibenzanthracene* formed colourless rhombic crystals, m. p. 234—235·5° (Found: C, 85·3; H, 5·5. $C_{20}H_{16}O_2$ requires C, 85·2; H, 5·4%); its *dipicrate* crystallised from benzene in deep-red needles, m. p. 183—184° (decomp.) (Found: C, 54·2; H, 2·9; N, 10·5. $C_{32}H_{22}O_{14}N_6$ requires C, 54·3; H, 3·0; N, 10·55%).

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177. "*Leaf Alcohol*" *and the Stereochemistry of the* cis- *and the* trans-n-*Hex*-3-*en*-1-*ols and* -n-*Pent*-3-*en*-1-*ols*.

By Leslie Crombie and Stanley H. Harper.

The stereochemistry of "leaf alcohol" is examined. The compound is shown to be *cis*-hex-3-enol, thus confirming the suggestion of Stoll and Rouvé. Takei's assignment of the *trans*-configuration to it is mistakenly based on the properties of a synthetic hexenol, which is not the true stereoisomer of "leaf alcohol" and is probably not homogeneous. Authentic *trans*-hex-3-enol is described and certain melting-point anomalies are removed.

The infra-red absorption spectra of *cis*- and *trans*-hex-3-enol are examined and the preparation of *cis*- and *trans*-pent-3-enol is described.

In connection with our investigations of the sterochemistry of cinerone (Harper, *J.*, 1946, **892**; Crombie and Harper, *Nature*, 1949, **164**, 534), jasmone (Crombie and Harper, forthcoming publication), and related compounds, it became necessary to have available specimens of the *cis*- and the *trans*-form of pent-3-enol and of hex-3-enol. One stereochemical form of hex-3-enol is widely distrubuted in nature as "leaf alcohol" (Walbaum, *J. für Chem.*, 1917, [ii], **96**, 245; Takei, Sakato, Ono, and Kuroiwa, *J. Agric. Chem. Soc. Japan*, 1938, **14**, 709; Bohnsack,

Ber., 1941, **74**, 1575; 1942, **75**, 72; 1943, **76**, 564). It is usually isolated from green-tea oil or from the tailings of Japanese peppermint oil, in which it occurs as the phenylacetate, and is used in perfumery since it possesses the characteristic smell of green grass and leaves. Although its structure as a hex-3-enol is fully established, its stereochemical configuration has been the subject of dispute (Takei, *ibid.*, 1940, **73**, 950; Stoll and Rouvé, *ibid.*, p. 1358). The synthesis of "leaf alcohol" by Stoll and Rouvé (*Helv. Chim. Acta*, 1938, **21**, 1542), through the semihydrogenation of hex-3-ynol with a colloidal palladium catalyst, strongly favoured the *cis*-configuration. This was further supported by the presence of bands at 1267 and 1655 cm.$^{-1}$ in its Raman spectrum (Ruzicka, Schinz, and Susz, *ibid.*, 1944, **27**, 1561; cf. Grédy, *Bull. Soc. chim.*, 1935, [v], **3**, 1101). However an isomeric sharper-smelling hexenol had been prepared by Ruzicka and Schinz (*Helv. Chim. Acta*, 1934, **17**, 1602) and by Takei, Imaki, and Tada (*Ber.*, 1935, **68**, 953) by Bouveault–Blanc reduction of ethyl sorbate, which was accepted as the stereoisomer of "leaf alcohol." The derivatives of this hexenol melted at lower temperatures than those of "leaf alcohol" (see the table; but for a more comprehensive list see Takei, Sakato, Ono, and Kuroiwa, *loc. cit.*), a fact which led Takei to reject the *trans*-configuration for the former and to regard it as the *cis*-, "leaf alcohol" becoming the *trans*-isomer.

Since the Bouveault–Blanc reduction of ethyl sorbate gave a poor yield we have prepared trans-*hex-3-enol* by the lithium aluminium hydride reduction of *trans*-hex-2-enoic acid.* This acid was made by the Knoevenagel condensation of *n*-butaldehyde with malonic acid, using triethanolamine as catalyst (Boxer and Linstead, *J.*, 1931, 740; Linstead, Noble, and Boorman, *J.*, 1933, 557). It is reasonable to assume that this reaction gives a *trans*-acid since Lane, Fentress, and Sherwood (*J. Amer. Chem. Soc.*, 1944, **66**, 545) prepared a pent-2-enoic acid from crotyl chloride, which from the conditions of its formation has the *trans*-configuration, and this was identical with the pent-2-enoic acid prepared by the Knoevenagel condensation of propaldehyde (Linstead, Noble, and Boorman, *loc. cit.*). It is therefore considered that this hex-2-enoic acid and the hex-3-enol prepared from it have the *trans*-configuration. This conclusion has been confirmed by Dr. F. Sondheimer (private communication; succeeding paper) who has obtained an identical hexenol by the reduction of hex-3-ynol with sodium in liquid ammonia, a process that is known to give the pure *trans*-ethenoid product (Campbell and Eby, *ibid.*, 1941, **63**, 216, 2683; Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 90; Greenlee and Fernelius, *J. Amer. Chem. Soc.*, 1942, **64**, 2505).

This *trans*-hex-3-enol was clearly different from Ruzicka and Schinz's hexenol for it had a powerful but pleasant chrysanthemum-like odour and its derivatives melted at higher temperatures (see the table). The 1-naphthylurethane of the alcohol prepared by the Bouveault–Blanc reduction depressed both the melting point of the 1-*naphthylurethane* of our *trans*-hex-3-enol and that of "leaf alcohol." The identity of Ruzicka and Schinz's hexenol is not certain, but it may be a mixture of hex-3-enols and hex-4-enols, for the derivative melted rather unsharply. It is relevant that Goldberg and Linstead (*J.*, 1928, 2343) showed that sodium amalgam reduction of sorbic acid gave a mixture of hex-2-enoic and hex-3-enoic acids ("hydrosorbic acid"), which had previously been regarded as a homogeneous substance. Furthermore, Fischer and Wiedmann (*Annalen*, 1936, **522**, 1) state that reduction of sorbaldehyde with sodium in ethanol gives a mixture of hex-3-enol (~66%) and hex-4-enol (~33%).

Although the melting points of the 1-naphthylurethane and 3:5-*dinitrobenzoate* of *trans*-hex-3-enol were very close to those of the corresponding derivatives of "leaf alcohol," on admixture large depressions were observed. The p-*nitrophenylurethane* and the p-*diphenylylurethane* of *trans*-hex-3-enol, however, melted at higher temperatures than the corresponding derivatives of "leaf alcohol." "Leaf alcohol" is clearly not *trans*-hex-3-enol. Furthermore these melting points invalidate Takei's argument and there is no doubt that from the method of synthesis, the Raman spectrum, and by exclusion "leaf alcohol" is *cis*-hex-3-enol.

We have examined the tailings from the distillation of Brazilian peppermint oil (*Mentha Arvensis*) as a likely source of "leaf alcohol," although we are not aware of its presence having been previously recorded. Distillation gave fractions containing ester and the richest was hydrolysed to yield an exceptionally pure specimen of "leaf alcohol." The steam-volatile oily acid failed to crystallise when seeded with phenylacetic acid, from which it would appear as if "leaf alcohol" is not present as the phenylacetate in Brazilian peppermint oil.

The infra-red spectra of few *cis–trans* pairs of olefinic hydrocarbons have been measured, but it is now generally accepted that an absorption band at 10·3 μ. is due to the flapping vibrations of the hydrogen atoms about a *trans*-double bond of the type

* Following current Journal practice the carboxyl group is not numbered in this and other acids.

Properties of cis- *and* trans-*hex*-3-*enol and* -*pent*-3-*enol*.

		"Leaf Alcohol." *cis*-.	Product from $LiAlH_4$ reduction. *trans*-.	Product from Bouveault–Blanc reduction.
Hex-3-enol	B. p.	66—67°/19 mm.	52—53°/9 mm.	59—60°/12 mm.*
	n_D^{20}	1·4384	1·4374	1·4370
1-Naphthylurethane	M. p.	69—70°	69—70°	61—63°
3 : 5-Dinitrobenzoate	M. p.	49°	47—48°	28°
p-Nitrophenylurethane	M. p.	72·5—73·5°	84—85°	—
p-Diphenylylurethane	M. p.	91·0—91·5°	99·0—99·5°	—
		cis-.	*trans*-.	
Pent-3-enol	B. p.	139—141°	136—137·5°	
	n_D^{20}	1·4386	1·4340	
1-Naphthylurethane	M. p.	88—89°	93°	

* Data taken from Ruzicka, Schinz, and Susz (*loc. cit.*) and from Takei, Imaki, and Tada (*loc. cit.*).

(cf. Rasmussen, Brattain, and Zucco, *J. Chem. Physics*, 1947, **15**, 135). There is some evidence too that an absorption maximum at 14 μ. in an olefinic hydrocarbon is to be associated with a *cis*-double bond of the type (Anderson and Seyfried, *Analyt. Chem.*, 1948, **20**, 998; Hall and Mikos, *ibid.*, 1949, **21**, 422; Hampton, *ibid.*, p. 923). However, information on the infra-red spectra of olefinic *cis-trans* pairs other than hydrocarbons is very sparse. Elaidic

Fig. 1.
cis-*Hex*-3-*enol* (*natural*).

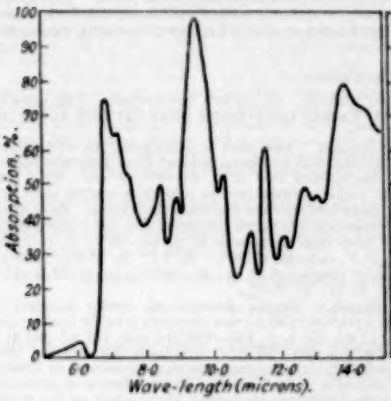
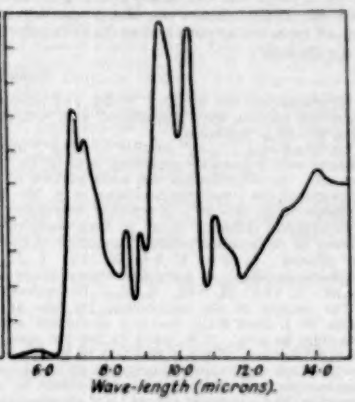


Fig. 2.
trans-*Hex*-3-*enol*.



acid (*trans*-) has a strong band at 10·3 μ. which is almost absent in oleic acid (*cis*-), and this band is also present in the spectrum of vaccenic acid (*trans*-). Both oleic and elaidic acid show absorption at 13·8—13·9 μ. (Rao and Daubert, *J. Amer. Chem. Soc.*, 1948, **70**, 1102). The infra-red spectra of *cis*- and *trans*-hex-3-enol therefore seemed of interest and were kindly determined by Miss I. M. Friedmann (see Figs. 1 and 2). The hydroxyl band at 9·5 μ. is strongly in evidence in both spectra, but the *trans*-alcohol shows a strong band at 10·3 μ. which is of very low intensity in the spectrum of the *cis*-alcohol, whereas the intensity of absorption at 13·9 μ. is markedly higher for the latter. These observations fall into line with the results quoted above and provide further evidence that "leaf alcohol" has the *cis*-configuration. Corresponding with the disappearance of the 10·3 μ. band characteristic of the *trans*-alcohol we find that a new band appears at 11·5 μ. in the spectrum of the *cis*-alcohol. There are also other minor differences between the two spectra. Observation of the bands at 10·3 μ., 11·5 μ., and 13·9 μ. may therefore be of considerable assistance in the assignment of geometrical configurations to compounds of the type $CH_3R{\cdot}CH{:}CH{\cdot}CH_2R'$, where R and R′ may be other than alkyl groups.

Three preparations of pent-3-enol have been described in the literature. Goethals (*Natuurwetensch. Tijds.*, **1937**, **19**, 184; *Bull. Acad. roy. Belg.*, **1937**, [v], **23**, 721; *Bull. Soc. chim. Belg.*, **1937**, **46**, 409) attempted to prepare pent-3-enol by the Bouveault–Blanc reduction of ethyl pent-2-enoate but even under the best conditions the product was a mixture containing some 25% of *n*-amyl alcohol. From the Raman data given by Goethals the unsaturated component appears to be *trans*. Goering, Cristol, and Dittmer (*J. Amer. Chem. Soc.*, **1948**, **70**, 3314) have described the preparation of a pent-3-enol of unspecified configuration by the lithium aluminium hydride reduction of methyl pent-2-enoate. Unfortunately these workers failed to characterise their product by crystalline derivatives, but from the method of preparation of the pent-2-enoic acid (hydrolysis of but-2-enyl cyanide, derived from crotyl chloride) we consider that it is largely or entirely *trans*. Finally Normant (*Compt. rend.*, **1948**, **226**, 733), by ring fission of 3-chloro-2-methyltetrahydrofuran with sodium, prepared a pent-3-enol which was not homogeneous. We had independently explored this route and shown that the product is a mixture of *cis*- and *trans*-pent-3-enol, and the evidence for this will be reported shortly. The mixed pent-3-enols were brominated in ether, and the dibromide dehydrobrominated by sodamide in liquid ammonia to give pent-3-ynol. From this, authentic pure *cis*- and *trans*-pent-3-enol have been prepared. *trans*-Pent-3-enol was made by reduction with sodium in liquid ammonia (cf. Sondheimer, *loc. cit.*), while the *cis*-isomer was obtained when the pentynol was hydrogenated over a palladium–calcium carbonate catalyst at room temperature. The two pent-3-enols had closely similar physical constants (see the table), but the 1-*naphthylurethane* of the *trans*-alcohol was a little higher-melting than the *cis*-derivative. The possibility that the *cis*-pent-3-enol contained a minor proportion of *trans*-isomer was considered, since it has been reported that semi-hydrogenation over Raney nickel or a supported nickel catalyst did not cause 100% *cis*-reduction (Henne and Greenlee, *J. Amer. Chem. Soc.*, **1943**, **65**, 2020). However, the proportion must be quite small, for the *cis*-hex-3-enoic acid derived from it was pure and we have found that the *trans*-acid is readily detected in derivatives of the *cis*-acid.

Experimental.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected. The infra-red absorption spectra were determined with a Grubb Parsons spectrometer using the pure liquids in a cell of 30—50 μ thickness.

cis-Hex-3-enol ("*Leaf Alcohol*").—The "leaf alcohol" used and a sample of its 3 : 5-dinitrobenzoate were generously presented to us by Dr. M. Stoll and had been isolated from Japanese peppermint oil. On redistillation the main portion of the alcohol had b. p. 65—67°/19 mm., n_D^{20} 1·4384. We prepared the 1-naphthylurethane, m. p. 69—70°, which crystallised as colourless needles from light petroleum (b. p. 60—80°), in which it was rather more soluble than the *trans*-derivative. In a search for derivatives differing in m. p. from those of *trans*-hex-3-enol we prepared also the *p-nitrophenylurethane* as colourless crystals of uncertain shape [from light petroleum (b. p. 40—60°)], m. p. 72·5—73·5° (Found: C, 59·0; H, 6·1; N, 11·1. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1; N, 10·6%), and the *p-diphenylylurethane* as colourless prisms [from light petroleum (b. p. 80—100°)], m. p. 91·0—91·5° (Found: C, 77·2; H, 7·25. $C_{19}H_{21}O_2N$ requires C, 77·25; H, 7·2%).

The sample of the high-boiling fraction of Brazilian *Mentha Arvensis* oil, kindly supplied by Messrs. W. J. Bush & Co., had b. p. above 200° and a portion (220 g.) was therefore roughly fractionated in vacuum to give: (i) b. p. up to 100°/20 mm. (11 g.), (ii) b. p. 100—120°/18 mm. (85 g.), (iii) b. p. 135—150°/18 mm. (54 g.), and (iv) b. p. 150—165°/18 mm. (52 g.). Fractions (iii) and (iv) gave saponification equivalents corresponding to 31 and 45% of ester respectively, calculated as hexenyl phenylacetate. Fraction (iv) was hydrolysed by adding it in portions to a warm solution of potassium hydroxide (20 g.) in water (75 ml.) and completing the hydrolysis by heating the mixture on the steam-bath for 2 hours. Next day the hydrolysate was steam-distilled and the first 400 ml. of distillate were extracted with ether. The extract was dried (K_2CO_3) and distilled through a short column to give "leaf alcohol" (6·2 g.), b. p. 154—157°, n_D^{20} 1·4383. The 1-naphthylurethane, m. p. 71·0—71·5°, was slightly purer than that prepared from Dr. Stoll's hexenol, crystallising more readily in superior form, but gave no m. p. depression on admixture. Continued steam-distillation yielded a yellow oil, b. p. above 200°, evidently a neutral constituent of the original oil. The alkaline solution was then acidified and again steam-distilled, to yield an oily acid which did not crystallise when seeded with phenylacetic acid. It has not been further examined.

trans-Hex-3-enol.—*trans*-Hex-2-enoic acid was prepared by the method of Linstead, Noble, and Boorman (*loc. cit.*) and purified by partial freezing and rejection of the liquid layer. An ethereal solution of the acid (2·80 g.) was added slowly to lithium aluminium hydride (0·95 g.) dissolved in anhydrous ether (50 ml.). The reaction was completed by refluxing for one hour, cooling, and addition of water to destroy the excess of lithium aluminium hydride. The ethereal layer was washed with dilute acid and alkali, and on distillation gave trans-*hex-3-enol* (1·61 g.), b. p. 51—53°/9 mm., n_D^{20} 1·4374 (Found: C, 72·0; H, 12·2. $C_6H_{12}O$ requires C, 71·9; H, 12·1%). The 1-*naphthylurethane* formed needles (from light petroleum), m. p. 69—70° (Found: C, 75·8; H, 7·2; N, 5·6. $C_{13}H_{15}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%), and when admixed with the 1-naphthylurethane of *cis*-hex-3-enol (1 : 1) melted at once when placed in a bath at 58°. The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 40—60°) in a freezing mixture and after one crystallisation had m. p. 43—46°; four

recrystallisations raised this to m. p. 47—48° (Found: C, 53·6; H, 4·95; N, 9·5. $C_{12}H_{11}O_3N$, requires C, 53·05; H, 4·8; N, 9·5%). The *p-nitrophenylurethane* had m. p. 84—85° (Found: C, 59·0; H, 6·15; N, 11·0%), and the *p-diphenylylurethane* had m. p. 99·5° (Found: C, 77·3; H, 7·15%) [these derivatives were prepared from *trans*-hex-3-enol made by a new method (to be published) which gave a 1-naphthylurethane and 3 : 5-dinitrobenzoate identical with those described above]. The anthraquinone-2-carboxylate, in our hands, proved an unsatisfactory derivative; it was formed in low yield, was difficult to obtain crystalline, was photosensitive, and often showed a double m. p. (49—50° and 68—70°).

Hexenol from the Bouveault–Blanc Reduction of Ethyl Sorbate.—We are indebted to Prof. L. Ruzicka for the gift of a small specimen of the 1-naphthylurethane of this hexenol (cf. Ruzicka, Schinz, and Susz, *loc. cit.*). It sintered at 59—60°, melted to a turbid yellow melt at 61—63·5°, which became clear at 64·5°.

Pent-3-ynol.—The *cis-trans*-mixture of pent-3-enols (74 g.), prepared by the ring fission of 3-chloro-2-methyltetrahydrofuran, was diluted with ether (75 ml.), and bromine (141 g.) added dropwise, the temperature being kept below 25°. The ether was then sucked off by a water pump. If the temperature is allowed to rise much above 25° there is a tendency for hydrogen bromide to be eliminated with the formation of 3-bromo-2-methyltetrahydrofuran. Meanwhile sodamide was prepared by dissolving sodium (70 g.) in liquid ammonia (1·5 l.) in the presence of an iron catalyst (Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120). The 3 : 4-dibromopentanol was then added rapidly to the stirred solution of sodamide in liquid ammonia and stirred for 4 hours. A layer of ether was then added and the ammonia allowed to evaporate overnight. Next morning ammonia solution (*d* 0·880) and then water were added; the aqueous layer was thoroughly extracted with ether, and the bulked extracts were washed and dried. Fractional distillation gave pent-3-ynol (24·3 g.), b. p. 154—157°, n_D^{25} 1·4554 (Found: C, 69·5; 69·4; H, 9·95, 9·7. Calc. for C_5H_8O: C, 71·4; H, 9·6%). The *1-naphthylurethane* formed needles [from light petroleum (b. p. 60—80°)], m. p. 119° (Found: C, 76·0; H, 6·1. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0%). A considerable quantity of a bromopentenol (3- or 4-bromopent-3-enol), containing vinyl bromide, was recovered from the higher-boiling fractions, b. p. 99°/14 mm., n_D^{25} 1·4897.

cis-Pent-3-enol.—Pent-3-ynol (52·5 g.) was hydrogenated at room temperature and atmospheric pressure in the presence of a palladium–calcium carbonate catalyst (1·5 g.; 10% of Pd) without use of a solvent. When 13·5 l. had been absorbed (Calc. for reduction to pentenol: 14·0 l.), filter col was added, and the catalyst removed by filtration and washed with a little ether. Careful distillation of the filtrate gave *cis-pent-3-enol* (39·8 g.), b. p. 139—142°, n_D^{25} 1·4387 (Found: C, 69·4; H, 11·8. $C_5H_{10}O$ requires C, 69·7; H, 11·7%). The *1-naphthylurethane* formed needles [from light petroleum (b. p. 60—80°)], m. p. 88—89° (Found: C, 75·2; H, 6·4. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·4%).

trans-Pent-3-enol.—Sodium (10 g.) was added to liquid ammonia (300 ml.) and then pent-3-ynol (5·0 g.) was added to the blue solution with stirring during 15 minutes. After stirring for a further 90 minutes ammonia solution (*d* 0·880) was added cautiously and the product set aside overnight to allow as much as possible of the ammonia to evaporate. Thorough extraction of the residue with ether, followed by washing, drying, and distillation, gave *trans*-pent-3-enol (3·0 g.), b. p. 136—137°, n_D^{25} 1·4340 (Found: C, 69·45; H, 11·6%). The *1-naphthylurethane* formed needles, m. p. 93° (Found: C, 75·55; H, 6·55; N, 5·6%). A 1 : 1 mixture with the *cis*-1-naphthylurethane melted at 75—80°.

We gratefully acknowledge grants from the Agricultural Research Council, the Central Research Fund of the University of London, the Royal Society, and the Chemical Society which have defrayed the expenses of this investigation. We are also indebted to Prof. L. Ruzicka, Dr. M. Stoll, and Messrs. W. J. Bush and Co. for gifts of materials.

KING'S COLLEGE (UNIVERSITY OF LONDON), STRAND, W.C.2. [*Received, November* 19th, 1949.]

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178. *Studies of Compounds related to Natural Perfumes. Part I. Concerning* cis- *and* trans-*Hex-3-en-1-ol.*

By FRANZ SONDHEIMER.

A convenient synthesis of hex-3-yn-1-ol (V) has been devised. Partial hydrogenation in the presence of palladium–calcium carbonate at room temperature gives an isomeric mixture of hex-3-en-1-ols, consisting mainly of the *cis*-isomer ("leaf alcohol"). Partial reduction of (V) with sodium in liquid ammonia gives exclusively *trans*-hex-3-en-1-ol (VIII), identical with that prepared by Crombie and Harper (preceding paper) and different from what had previously been considered the *trans*-isomer.

The acetylenic alcohol (V) is converted into the bromide (VI), which on attempted condensation with sodium acetylide in liquid ammonia undergoes dehydrobromination to hex-1-en-3-yne (VII). Similarly the ethylenic bromide (IX) with sodium acetylide gives hexa-1 : 3-diene (X).

In connexion with synthetical studies designed to elucidate the exact stereochemical configuration of the important violet-leaf constituents nona-2 : 6-dienol (I) and nona-2 : 6-

(I.) $CHEt{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$ $CHEt{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH{\cdot}CHO$ (II.)

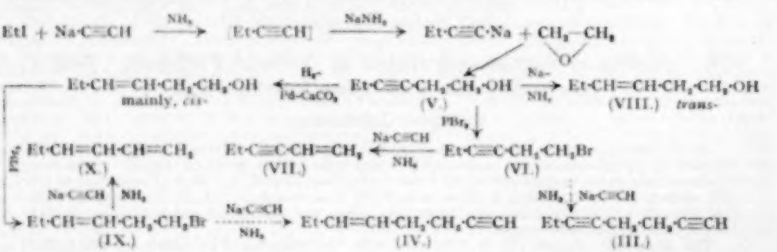
dienal (II) (Ruzicka, Schinz, *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1602; 1944, **27**, 1561; Takei *et al.*, *Bull. Agric. Chem. Soc. Japan*, 1938, **14**, 64; *Chem. Zentr.*, 1938, II, 3696; Hunsdiecker,

Chem. Ber., 1947, **80**, 137), octa-1 : 5-diyne (III) and oct-5-en-1-yne (IV) were required. It was hoped to prepare these hydrocarbons from hex-3-yn-1-ol (V) and hex-3-en-1-ol by the action of sodium acetylide in liquid ammonia on the respective bromides (VI) and (IX). In fact it was found that these bromides were very readily dehydrobrominated to the hydrocarbons (VII) and (X) respectively (cf. Vaughn, Hennion, Vogt, and Nieuwland, *J. Org. Chem.*, 1937, **2**, 13), and the required hydrocarbons (III) and (IV) could not be obtained by this route. The diacetylene (III) was subsequently synthesised by a different method, and was successfully converted into nona-2 : 6-dienol (I) and the corresponding aldehyde (II) (Sondheimer, forthcoming publication). However, some interesting results were obtained in the present study concerning the *cis*- and *trans*-isomers of hex-3-en-1-ol and, as there exists some confusion about these compounds in the literature, it seemed desirable to record the results.

Hex-3-yn-1-ol (V) had previously been obtained from but-1-ynylmagnesium bromide and ethylene oxide (Stoll and Rouvé, *Helv. Chim. Acta*, 1938, **21**, 1542; Takei, Ono, and Sinosaki, *Ber.*, 1940, **73**, 950), the overall yield from the starting material, methyl ethyl ketone, being only *ca.* 1—6%. It may also be obtained by the dehydrobromination of the dibromide of hex-3-en-1-ol (Takei, Ono, and Sinosaki, *loc. cit.*; Bohnsack, *Ber.*, 1941, **74**, 1575; Stoll and Commarmont, *Helv. Chim. Acta*, 1949, **32**, 597). When ethyl iodide was treated in liquid ammonia with sodium acetylide (prepared directly from sodium and acetylene; cf. Raphael and Sondheimer, *J.*, 1950, 115), the highly volatile but-1-yne so formed was not isolated but was converted into the sodio-derivative by the addition of one mole of sodamide. Reaction with ethylene oxide then gave the required hex-3-yn-1-ol (V) (3 : 5-dinitrobenzoate; α-*naphthylurethane*) in 47% yield. After this work had been completed, the reaction between ethylene oxide and the sodio-derivative of 1-butyne (prepared separately) in liquid ammonia solution was reported by Newman and Wotiz (*J. Amer. Chem. Soc.*, 1949, **71**, 1292), who obtained hex-3-yn-1-ol in 48% yield.

The acetylenic carbinol was converted into the *bromide* (VI) by phosphorus tribromide, using various amounts of pyridine, but only in poor yield (cf. Tchao, *Bull. Soc. chim.*, 1933, **53**, 1533; Newman and Wotiz, *loc. cit.*, for the successful bromination of α-acetylenic primary alcohols). The same difficulty in the direct bromination of the β-acetylenic alcohol but-3-yn-1-ol was encountered by Jones and Whiting (private communication), who were however successful in brominating the corresponding toluene-*p*-sulphonate. The acetylenic bromide (VI) was treated with an excess of sodium acetylide in liquid ammonia, whereupon it underwent mainly dehydrobromination; no appreciable amount of the required diacetylene (III) was formed, and hex-1-en-3-yne (VII) could be isolated.

Attention was then turned to the partial reduction of hex-3-yn-1-ol (V). The hex-3-en-1-ol which could thereby be formed is of interest as the starting material for the synthesis of nona-2 : 6-dienol (I) and the corresponding aldehyde (II) (for references see above), and also of the important perfume jasmone (Treff and Werner, *Ber.*, 1935, **68**, 640; Hunsdiecker, *Ber.*, 1942,



75, 460). The *cis*-isomer is also of importance, as it is found widely distributed in many species of plants. It possesses the characteristic "green" odour of leaves and grass, and is usually termed "leaf alcohol."* Partial hydrogenation of acetylenes in the presence of a colloidal palladium or Raney nickel catalyst is known to give the *cis*-ethylenic compounds (*inter al.*,

* There exists some controversy in the literature regarding the stereochemical configuration of the natural hex-3-enol (Stoll and Rouvé, *loc. cit.*; *Ber.*, 1940, **73**, 1358; Takei, Ono, and Sinosaki, *loc. cit.*; Ruzicka, Schinz, and Susz, *Helv. Chim. Acta*, 1944, **27**, 1561; Crombie and Harper, *loc. cit.*), but previous evidence together with that presented in this paper clearly points to the *cis*-configuration.

Bourguel, *Bull. Soc. chim.*, 1929, **45**, [iv], 1067; Campbell and Eby, *J. Amer. Chem. Soc.*, 1941, **63**, 216, 2683; Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 148), and the catalytic semi-hydrogenation of hex-3-yn-1-ol has already been investigated by Stoll and Rouvé and by Takei, Ono, and Sinosaki (*locc. cit.*). The Swiss workers, using colloidal palladium, obtained a hex-3-enol, which was assigned the *cis*-configuration and shown to be identical with the natural hexenol (" leaf alcohol ") as the 3 : 5-dinitrobenzoate after " five laborious crystallisations " had m. p. 44·5—46°, undepressed on admixture with the natural derivative (m. p. 48—48·5°). The Japanese workers using a palladium–barium sulphate catalyst found that the properties of the hydrogenation product were dependent on the temperature of hydrogenation, the pure natural hex-3-enol being formed at −18°.

On hydrogenation of hex-3-ynol (V) at room temperature in the presence of palladium–calcium carbonate, the uptake of hydrogen practically stopped after 1 mole of gas had been absorbed. The hex-3-enol so obtained was very similar to that reported by Stoll and Rouvé, both in its physical properties and in the fact that the 3 : 5-dinitrobenzoate required seven crystallisations to achieve constant melting point (48—48·5°; undepressed on admixture with the derivative of natural hexenol, m. p. 49—50°). The α-naphthylurethane also needed three crystallisations to reach constant melting point (69—69·5°; undepressed on admixture with the natural derivative, m. p. 70—70·5°). It thus seemed that, although the hex-3-en-1-ol obtained by catalytic hydrogenation consisted predominantly of the *cis*-isomer, it contained an impurity, possibly the *trans*-isomer. This has been confirmed by its infra-red spectrum described below.

A hex-3-en-1-ol has been prepared by the Bouveault–Blanc reduction of ethyl sorbate (Ruzicka and Schinz, *Helv. Chim. Acta*, 1934, **17**, 1602; Takei, Imaki, and Tada, *Ber.*, 1935, **68**, 953), differing from the natural material by its sharper smell and the lower melting points of its derivatives (3 : 5-dinitrobenzoate, m. p. 28°; α-naphthylurethane, m. p. 61—63°). It was considered to be stereoisomeric with the natural (*cis*-)hexenol, *i.e.*, to have the *trans*-configuration (Ruzicka, Schinz, and Susz, *Helv. Chim. Acta*, 1944, **27**, 1561; cf. Takei, Imaki, and Tada, *loc. cit.*). Partial reduction of acetylenic hydrocarbons and tertiary carbinols by means of sodium in liquid ammonia has been shown to give the *trans*-ethylenic compounds (Campbell and Eby, and Campbell and Campbell, *locc. cit.*). When the primary alcohol hex-3-yn-1-ol (V) was treated in this way, the trans-*hex-3-en*-1-*ol* (VIII) so formed in good yield was found to be different from that obtained by the Bouveault–Blanc reduction of ethyl sorbate. Its derivatives (*3 : 5-dinitrobenzoate*, m. p. 46—46·5°; *α-naphthylurethane*, m. p. 68—69°) were considerably higher-melting than those of the Bouveault–Blanc product and, although the melting points of the *trans*-hexenol derivatives were nearly identical with those of the *cis*-isomer, considerable depressions were observed on admixture.

Independently of this work, Crombie and Harper (*loc. cit.*) found that both by the action of lithium aluminium hydride on *trans*-pent-2-ene-1-carboxylic acid, and also by the ring fission of the α-form of 3-chloro-2-ethyltetrahydrofuran, a *trans*-hex-3-enol was obtained, also differing from that described by Ruzicka and Schinz. The melting points of the derivatives of the *trans*-hexenol reported by Crombie and Harper are identical with those of the *trans*-hexenol (VIII) described in the present communication, and identity was established by mixed-melting-point determinations. It is highly probable that the so-called *trans*-isomer of Ruzicka and Schinz was not homogeneous. Nevertheless it must have contained a considerable percentage of the *trans*-hexenol, as the nona-2(*trans*) : 6(*trans*)-dienal prepared from it was shown to be identical with a sample prepared by an independent method (Hunsdiecker, *Chem. Ber.*, 1947, **80**, 137).

The infra-red spectra of the *cis*- and *trans*-hex-3-enols have already been recorded and discussed by Crombie and Harper (*loc. cit.*). The spectrum of the *trans*-isomer (VIII) obtained by the sodium–liquid ammonia reduction of hexynol (Fig. 1) is closely similar to that previously recorded, showing the typical strong " *trans* "-absorption band at 10·3 μ. (Rasmussen, Brattain, and Zucco, *J. Chem. Physics*, 1947, **15**, 135). The infra-red spectrum of the natural (*cis*-)hex-3-enol has been given by Crombie and Harper (*loc. cit.*), while Fig. 2 shows the spectrum of the hex-3-enol obtained by the catalytic hydrogenation of hexynol. The bands at 11·5 and 13·8 μ. in Fig. 2 are typical for the *cis*-isomer, not being shown by the *trans*-form. On the other hand, the " *trans* "-band at 10·3 μ. is also quite marked. From these data, combined with the fact that on repeated crystallisation the *cis*-derivatives are obtained, it is concluded that catalytic hydrogenation of hexynol (V) under the conditions employed gives a *cis-trans*-mixture of hex-3-en-1-ols, consisting predominantly of the *cis*-isomer.

The hex-3-enol (mainly *cis*-) was converted into the bromide (IX), and this was treated with

sodium acetylide in liquid ammonia. Again no appreciable amount of the hydrocarbon (IV) could be isolated, dehydrobromination to hexa-1 : 3-diene (X) (determined quantitatively by its ultra-violet light absorption maximum at 2280 A.) being the principal reaction.

FIG. 1.

trans-Hex-3-enol from Na reduction.

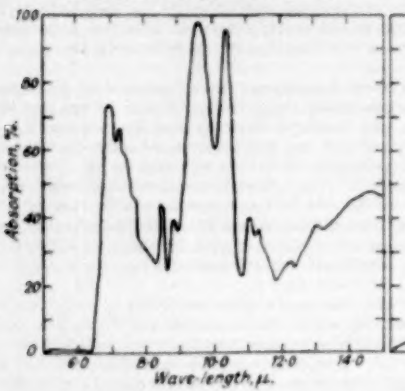
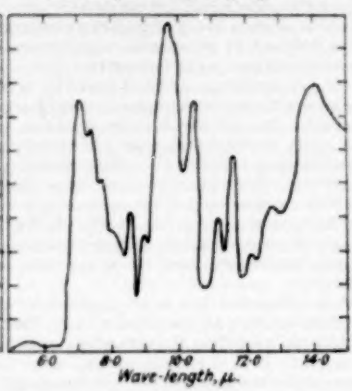


FIG. 2.

Hex-3-enol from catalytic hydrogenation.



EXPERIMENTAL.

Hex-3-yn-1-ol (V).—Sodium (40 g., 1·74 g.-mols.) was added in small pieces to liquid ammonia (1·5 l.) through which acetylene was bubbled, with stirring and cooling (alcohol–carbon dioxde). The acetylene flow was stopped at the exact moment when the blue colour disappeared after the last piece of sodium had been added (to ensure that no excess of acetylene was present in solution), and ethyl iodide (250 g., 1·6 g.-mols.) in dry ether (250 c.c.) was introduced during the course of 45 minutes. The cooled reaction mixture was stirred for 4 hours and the 1-butyne so formed was converted into the sodio-complex by addition, in several portions, of a cooled sodamide suspension in liquid ammonia (1 l.), made from sodium (40 g.), the ferric nitrate catalyst of Vaughn, Vogt, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 2120) being used. After another hour's stirring, ethylene oxide (141 g., 3·2 g.-mols.) was added all at once, and the reaction mixture was stirred for 24 hours, the temperature being held at *ca.* −40°. Ammonium chloride (120 g.) was gradually introduced, and the ammonia evaporated on the steam-bath. Water and ether were added to the residue, and the aqueous layer washed twice with ether. The combined ethereal extracts, after being washed with a small volume of water, were dried ($MgSO_4$) and evaporated. A preliminary distillation, followed by fractionation through a Dufton column, then gave hex-3-yn-1-ol (73·2 g., 47% calc. on ethyl iodide), b. p. 163—164°/772 mm., 73·5—74·5°/23 mm., n_D^{17} 1·4579 (Stoll and Rouvé, *Helv. Chim. Acta*, 1938, **21**, 1542, give b. p. 65·5—66°/12 mm., n_D^{20} 1·4530). The 3 : 5-dinitrobenzoate after one crystallisation from light petroleum (b. p. 60—80°) had constant m. p. 73—74° (Found: C, 53·6; H, 4·1; N, 9·65. Calc. for $C_{13}H_{12}O_6N_2$: C, 53·4; H, 4·1; N, 9·6%) (Newman and Wotiz, *loc. cit.*, give m. p. 72—73°; Stoll and Commarmont, *loc. cit.*, give m. p. 75—76° and 80—81°). The *α-naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in small needles, m. p. 84—85° (Found: C, 76·45; H, 6·4; N, 5·35. $C_{17}H_{17}O_2N$ requires C, 76·35; H, 6·4; N, 5·25%). In addition a higher-boiling product (13 g.) was obtained, b. p. 116—120°/23 mm., n_D^{17} 1·4628, which was not further investigated.

1-Bromohex-3-yne (VI).—Phosphorus tribromide (27 g.) in dry ether (15 c.c.) was slowly added to a cooled and stirred solution of hex-3-yn-1-ol (16 g.) in ether (65 c.c.), the temperature being kept at −5°. After being stirred at −5° for a further 90 minutes, the reaction mixture was poured on ice and water. The organic layer was washed with sodium hydrogen carbonate solution and water, and dried. Removal of ether, followed by distillation of the residue, gave *1-bromohex-3-yne* (3·75 g., 14%) as a colourless liquid, b. p. 63·5—65·5°/18 mm., $n_D^{17.5}$ 1·4890 (Found: Br, 49·1. C_6H_9Br requires Br, 49·6%).

In another experiment, the general conditions of Tchao (*loc. cit.*) were employed. Phosphorus tribromide (14·5 g.) was added dropwise to a cooled mixture of pyridine (0·6 g.) and hex-3-ynol (12·6 g.), with constant stirring during 30 minutes. The reaction mixture was then heated under reflux on the steam-bath for 3 hours, and the product isolated as before. This yielded the bromide (2·4 g., 12%), b. p. 67—68°/25 mm., n_D^{17} 1·4931. In addition, a higher-boiling liquid was obtained, b. p. 99—100°/25 mm., n_D^{17} 1·5222, giving analytical figures correct for the hydrogen bromide adduct of 1-bromohex-3-yne (Found: Br, 65·55. $C_6H_{10}Br_2$ requires Br, 66·05%).

The conditions of Juvala (*Ber.*, 1930, **63**, 1990) were also employed, using hex-3-ynol (16 g.), pyridine (2·8 g.), and phosphorus tribromide (17·4 g.). This gave a mixed product which could only have contained a very small proportion of the required bromide. Hex-3-en-1-ol can be successfully converted into the bromide under these conditions (see below).

Hex-1-*en*-3-*yne* (VII).—A suspension of sodium acetylide in liquid ammonia (100 c.c.) was prepared by adding sodium (1·2 g.) to the stirred and cooled (alcohol–carbon dioxide) liquid, through which acetylene was being passed. As soon as the colour was discharged, the acetylene flow was reduced, and the acetylenic bromide (3·2 g.) in dry ether (3 c.c.) was added. The cooled reaction mixture was stirred for a further 5 hours, ammonium chloride (4 g.) added, and the solvent removed on the steam-bath. Water and ether were added to the residue, the ethereal layer was washed with sodium hydrogen carbonate solution and water, and dried. The solvent was removed through a short Vigreux column, and the residue distilled. This yielded hex-1-en-3-yne (0·5 g.) as a colourless liquid, b. p. 83—85°/762 mm., n_D^{15} 1·449 (Found: C, 90·45; H, 10·1. Calc. for C_6H_8: C, 89·95; H, 10·05%) (Jacobson and Carothers, *J. Amer. Chem. Soc.*, 1933, **55**, 1622, give b. p. 84·5—85·3°/758 mm., n_D^{25} 1·4522). The distillation residue (0·3 g.) consisted of a viscous brown gum.

Catalytic Partial Hydrogenation of Hex-3-*yn*-1-*ol* (V).—The acetylenic carbinol (14·7 g.) in methyl acetate (30 c.c.) was shaken with Raney nickel for 1 hour to remove the small amount of catalyst poison present. The metal was filtered off and well washed with methyl acetate. The filtrate was shaken in hydrogen in the presence of palladium–calcium carbonate (1·5 g.; 5% of Pd). About 3 l. of gas were rapidly absorbed during 1 hour, whereafter the uptake slowed down. After the absorption of 3590 c.c. of gas (15°/758 mm.; 0·99 mole) the uptake had practically stopped. The catalyst was filtered off, the solvent removed, and the residue distilled. This yielded impure *cis*-hex-3-en-1-ol (13·1 g.), b. p. 156—157°/765 mm., 74—75°/29 mm., n_D^{15} 1·4430, having an odour very similar to that of a sample of natural (*cis*-)hexenol [Stoll and Rouvé, *loc. cit.*, give b. p. 59—61°/12·5 mm., n_D^{15} 1·4373, for the hexenol obtained by catalytic hydrogenation; Ruzicka, Schinz, and Susz, *loc. cit.*, give b. p. 58—58·5°/12 mm., n_D^{15} 1·4380, for pure natural (*cis*-)hexenol regenerated from the crystalline allophanate].

Derivatives of cis-Hex-3-*en*-1-*ol*.—The above isomeric mixture was converted into the 3 : 5-dinitrobenzoate in the usual manner. After one crystallisation from light petroleum (b. p. 40—60°) it formed long needles, m. p. 34—35°. After another six crystallisation from this solvent or pentane, the 3 : 5-dinitrobenzoate of *cis*-hexenol was obtained, having constant m. p. 48—48·5° (Found: C, 53·1; H, 4·85; N, 9·65. Calc. for $C_{13}H_{14}O_6N_2$: C, 53·05; H, 4·8; N, 9·5%); this m. p. was not depressed on admixture with a sample (m. p. 49—50°) obtained from the natural hexenol.

The α-naphthylurethane prepared from the isomeric mixture had, after two crystallisations from light petroleum (b. p. 40—60°), m. p. 65°, and after another crystallisation the pure α-naphthylurethane of *cis*-hexenol was obtained as long needles, having constant m. p. 69—69·5° (Found: C, 75·95; H, 7·2; N, 4·9. Calc. for $C_{17}H_{19}O_2N$: C, 75·8; H, 7·1; N, 5·2%); this m. p. was not depressed on admixture with a specimen (m. p. 70—70·5°) obtained from the natural alcohol.

trans-*Hex*-3-*en*-1-*ol* (VIII).—Hex-3-yn-1-ol (4·9 g.), dissolved in dry ether (5 c.c.), was gradually added to a stirred and cooled (alcohol–carbon dioxide) solution of sodium (4·6 g.) in liquid ammonia (200 c.c.). Stirring was continued for a further 2 hours, whereafter the blue reaction mixture was decomposed with ammonium chloride (15 g.). The ammonia was evaporated off on the steam-bath, water and ether were added to the residue, the aqueous layer was once more extracted with ether, and the combined organic extracts were washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The dried solution was evaporated. Distillation of the residue then gave trans-*Hex*-3-*en*-1-*ol* (3·7 g., 75%) as a colourless mobile liquid, b. p. 152—153·5°/762 mm., n_D^{15} 1·4406, possessing a characteristic odour distinctly different from the "green" odour of the *cis*-isomer (Found: C, 72·0; H, 12·15. $C_6H_{12}O$ requires C, 71·95; H, 12·1%) (Ruzicka, Schinz and Susz, *loc. cit.*, give b. p. 58·5—60°/12 mm., n_D^{15} 1·4376, for the "*trans*"-isomer obtained by the Bouveault–Blanc reduction of ethyl sorbate).

The 3 : 5-*dinitrobenzoate* was formed in quantitative yield, having m. p. 45—46°; after one crystallisation from light petroleum (b. p. 40—60°) it formed needles having constant m. p. 46—46·5° (Found: C, 53·1; H, 4·9; N, 9·55. $C_{13}H_{14}O_6N_2$ requires C, 53·05; H, 4·8; N, 9·5%). This m. p. was not depressed on admixture with a sample (m. p. 47°) derived from the lithium aluminium hydride reduction of *trans*-pent-2-ene-1-carboxylic acid (Crombie and Harper, *loc. cit.*). On admixture with the *cis*-derivative (m. p. 48—48·5°) described above, the m. p. was 33—35°.

The *α-naphthylurethane* after one crystallisation from light petroleum (b. p. 40—60°) formed needles, m. p. 68—69°, not raised by further crystallisation (Found: C, 75·55; H, 7·1; N, 5·35. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%). The m. p. was not depressed on admixture with a sample (m. p. 68·5—69·5°) prepared by Crombie and Harper (*loc. cit.*). On admixture with the "*trans*"-derivative (m. p. 61—63°), prepared from ethyl sorbate (Ruzicka, Schinz, and Susz, *loc. cit.*), the m. p. was 51—53°. On admixture with the *cis*-derivative (m. p. 69—69·5°) described above, the m. p. was 56—60°.

Hexa-1 : 3-*diene* (X).—The hex-3-enol (mainly *cis*-) obtained from the catalytic hydrogenation of the acetylene was converted into the bromide (IX) by the general method of Juvala (*loc. cit.*), as has already been described for the natural (*cis*-)hexenol (Treff and Werner, *loc. cit.*; Hunadiecker, *Ber.*, 1942, **75**, 460). The 1-bromohex-3-ene so obtained in *ca.* 50% yield had b. p. 49—51°/20 mm., n_D^{15} 1·473.

The ethylenic bromide (3·2 g.) was treated with sodium acetylide (from 1·2 g. of sodium) in liquid ammonia (100 c.c.) as described above for the acetylenic bromide. The reaction was allowed to proceed for 3·5 hours, and the mixture was then carefully poured on ice and *n*-hexane (without evaporating the ammonia, so as not to lose any of the volatile product). The organic layer was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). The solvent, containing the hexa-1 : 3-diene (Prévost, *Ann. Chim.*, 1928, **10**, 176; *Bull. Soc. chim.*, 1941, **8**, 89) was carefully distilled off through a Dufton column, until the distillation temperature reached 75°. The residue (0·25 g.) was dark and viscous, and could not be distilled. The hexane distillate (150 c.c.) had light absorption: Maximum, 2280 A.; $E_{1cm}^{1\%}$ = 14·5. This corresponds to a *ca.* 0·97-g. content of hexa-1 : 3-diene (60% yield), assuming ε = 22,000 for the pure diene.

The author thanks Sir Ian Heilbron, D.S.O., F.R.S., for his interest in this work, and Drs. S. H. Harper and L. Crombie for interesting discussions and samples used for mixed-m. p. determinations. He is also indebted to the Department of Scientific and Industrial Research for a

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7.
CONVERSE MEMORIAL LABORATORY, HARVARD UNIVERSITY,
CAMBRIDGE 38, MASS., U.S.A. [*Received, November 30th*, 1949.]

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179. *The Solubility Products of Ferrous and Ferrosic Hydroxides.*

By T. V. ARDEN.

Values of $2{\cdot}4 \times 10^{-14}$ and $6{\cdot}4 \times 10^{-18}$ for the solubility products of ferrous hydroxide and freshly precipitated green ferrosic hydroxide have been obtained by potentiometric titration with sodium hydroxide in sulphate solution, using a glass electrode.

THE precipitation of ferrous hydroxide has been widely studied, and the solubility product determined by a variety of methods. The highest value recorded, 7×10^{-12}, was obtained by Schrager (*Coll. Czech. Chem. Comm.*, **1929**, **1**, 275), while the lowest, $2{\cdot}5 \times 10^{-15}$, was given by Bödlander (*Z. Elektrochem.*, **1900**, **8**, 840). The latter value was confirmed by Britton (*J.*, 1925, **127**, 2110), by potentiometric titration of ferrous sulphate with sodium hydroxide, using a hydrogen electrode. The same method was used by Elder (*Trans. Amer. Electrochem. Soc.*, 1930, 57) who obtained a figure of $4{\cdot}8 \times 10^{-16}$. Conductivity measurements of saturated ferrous hydroxide solutions were used by Lamb (*J. Amer. Chem. Soc.*, 1910, **32**, 1214), and by Murata (*J. Soc. Chem. Ind. Japan*, 1932, **35**, 523), to calculate values of $9{\cdot}9 \times 10^{-16}$ and $2{\cdot}9 \times 10^{-15}$ respectively. Shipley and McHaffie (*Canadian Chem. Met.*, 1924, **8**, 5, 121) determined the solubility product of ferrous hydroxide as $3{\cdot}9 \times 10^{-15}$, from observations of the rate of corrosion of metallic iron in oxygen-free water. The solubilities of metallic iron in pure water, and in potassium hydroxide solution, were shown by Bineau (*Compt. rend.*, 1879, **41**, 509) and Krassa (*Z. Elektrochem.*, 1909, **15**, 491) to be $7{\cdot}5 \times 10^{-6}$ and $2{\cdot}8 \times 10^{-5}$ respectively, giving solubility products of $2{\cdot}0 \times 10^{-12}$ and $8{\cdot}7 \times 10^{-14}$, assuming complete ionisation. Whitman, Russell, and Davis (*J. Amer. Chem. Soc.*, 1925, **47**, 70) showed that ferrous hydroxide is only 30% ionised in saturated solution, the undissociated molecules being in true solution. The solubility of metallic iron in pure water at 25° was found to be $6{\cdot}7 \times 10^{-6}$, in agreement with the results of Bineau; but the solubility product, calculated from determinations of the pH of the saturated solution, was $3{\cdot}2 \times 10^{-14}$. A recalculation of Bineau's and Krassa's results, with allowance for the degree of ionisation of ferrous hydroxide, gives values of $4{\cdot}1 \times 10^{-14}$ and $2{\cdot}6 \times 10^{-14}$, respectively, for the solubility product.

The product of the reaction of pure ferrous sulphate solution with alkali is a white gelatinous precipitate, which becomes green in the presence of traces of ferric salts, owing to the presence of ferrosic hydroxide. The green compound is formed at a pH (6·4 in 0·05M-solution) considerably lower than that of pure ferrous hydroxide (8·1 in 0·05M-solution); and it is therefore necessary, in studying the precipitation of ferrous hydroxide, to eliminate both ferric iron and free oxygen from the system. It is extremely difficult to remove all traces of Fe^{+++}, and in a titrimetric procedure failure to prevent oxidation would result in low values for the solubility product. In the case of Britton's experiments, it was stated that air was not completely excluded. In methods based upon determinations of the solubility of iron in water (Bineau, Krassa, Lamb, Murata, and Whitman) the effect of traces of oxygen would be to raise the apparent solubility product; but the resulting errors would be small, since the solutions produced by this method are sufficiently alkaline to render the solubility of ferric iron negligible. The true solubility product of ferrous hydroxide therefore appears to be of the order of 10^{-14}, and results which are considerably lower than this figure are likely to have been influenced by oxidation.

The object of this work has been to determine $K_{Fe(OH)_2}$ from measurements of the changes in pH during a titration of ferrous sulphate with sodium hydroxide, in the complete absence of ferric iron or oxygen. In addition, the precipitation of ferrosic hydroxide has been studied, by titrations of mixtures of ferric and ferrous sulphates, in varying ratios. Titrations have also been carried out in the presence of atmospheric oxygen, to demonstrate the large errors which are caused in these conditions.

EXPERIMENTAL.

Ferrous Sulphate Solution.—A stock solution of 0·05M-ferrous sulphate, containing 0·05M-H_2SO_4, was prepared from pure metallic iron, and AnalaR sulphuric acid. It was impossible to maintain this

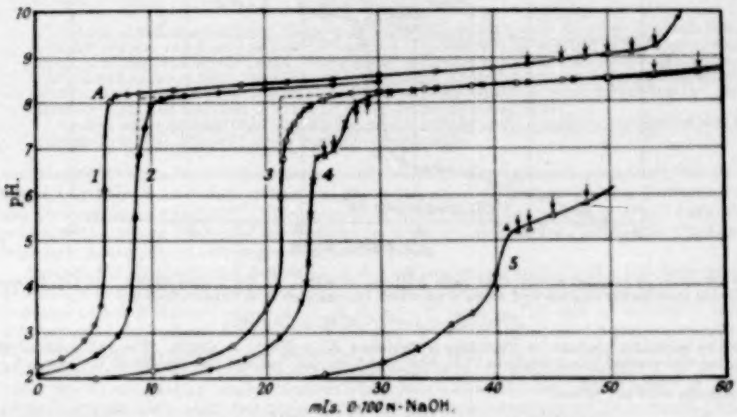
solution in a fully reduced condition, and a further reduction was therefore carried out immediately before each titration, by boiling a measured portion of the solution with metallic iron or magnesium in the sealed titration vessel. The experiment was then carried out under an atmosphere of hydrogen, the passage of which also served to agitate the solution. When iron was used for the reduction, the total ferrous content of the solution was determined at the end of the experiment; when magnesium was used, no interference with the titration was caused, since the step in the titration curve caused by the precipitation of magnesium hydroxide occurred at pH 10·5, after the completion of the ferrous reaction.

Ferric Sulphate Solution.—A solution containing 0·033M-ferric sulphate and 0·05M-H_2SO_4 was prepared by dissolving metallic iron in sulphuric acid, and oxidising with AnalaR hydrogen peroxide. The excess of peroxide was removed by prolonged boiling, and the solution was de-aerated immediately before each use by the prolonged passage of hydrogen.

Sodium Hydroxide Solution.—A solution (0·100N.) of sodium hydroxide was de-aerated by the prolonged passage of hydrogen immediately before each experiment.

Ferrous Hydroxide Precipitation.—A portion of the stock ferrous solution, initially at pH 1·5, was reduced and titrated with sodium hydroxide at 20°, the pH being determined by means of a glass electrode and a dip-type calomel half-cell. The electrode system was standardised before and after each experiment at pH 3·97 and 9·18, no results being accepted unless the four standardisation readings agreed within pH 0·05. After each addition of alkali, the pH was allowed to reach equilibrium. In the early stages of the titration, this process took place rapidly, but during the final stages of precipitation the pH dropped slowly to the values shown. (The direction and magnitude of changes of pH with time

FIG. 1.



are indicated by arrows touching the curves.) In the complete absence of ferric iron, sharp inflexions occurred at the point corresponding to the first permanent white precipitate (*A*, Fig. 1, Curve 1). In the presence of small traces of Fe^{+++}, the inflexions were less clearly defined (Fig. 1, Curves 2 and 3), and the formation of ferrous hydroxide was preceded by formation of traces of green ferrosic hydroxide. The true pH of first precipitation could nevertheless be determined by extrapolation of the horizontal and vertical portions of the curves. When sufficient ferric iron was present to give a definite green colour to the precipitate, the resultant curves were considerably distorted (Fig. 1, Curve 4) and were not used for the calculation of results. In a typical experiment, 50 ml. of 0·0500M-ferrous sulphate solution were reduced with magnesium, and titrated with 0·100N-sodium hydroxide. The point of first precipitation (*A*, Fig. 1, Curve 1) occurred after the addition of 6·1 ml. of alkali, when the total volume was 56·1 ml. The concentration of ferrous iron, $[Fe^{++}]$, is $0{\cdot}05 \times 50/56{\cdot}1 = 4{\cdot}48 \times 10^{-2}$. The pH was then 8·10, and since K_w at 20° is $10^{-14\cdot18}$, $[OH^-]$ is $10^{-5\cdot92}$.

Then $K = [Fe^{++}] \times [OH^-]^2 = 4{\cdot}48 \times 10^{-2} \times 10^{-11\cdot84} = 3{\cdot}1 \times 10^{-14}$, where K is the apparent solubility product, assuming complete dissociation of ferrous sulphate, and neglecting activity corrections.

The following results are calculated from curves in which the distortion is less than in curve 3 (Fig. 1)

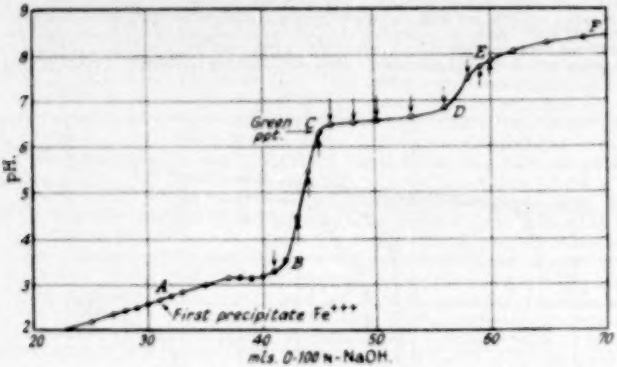
Expt.	$[Fe^{++}]$ at *A*.	pH.	$[OH^-]$.	Solubility product.
1	$4{\cdot}48 \times 10^{-2}$	8·10	$10^{-5\cdot92}$	$3{\cdot}1 \times 10^{-14}$
2	$3{\cdot}24 \times 10^{-2}$	8·15	$10^{-5\cdot85}$	$2{\cdot}8 \times 10^{-14}$
3	$4{\cdot}23 \times 10^{-2}$	8·00	$10^{-6\cdot18}$	$1{\cdot}9 \times 10^{-14}$
4	$3{\cdot}5 \times 10^{-2}$	8·10	$10^{-5\cdot92}$	$2{\cdot}4 \times 10^{-14}$
5	$8{\cdot}10 \times 10^{-3}$	8·44	$10^{-5\cdot56}$	$3{\cdot}0 \times 10^{-14}$
6	$8{\cdot}10 \times 10^{-3}$	8·40	$10^{-5\cdot60}$	$2{\cdot}2 \times 10^{-14}$
7	$3{\cdot}96 \times 10^{-3}$	8·5	$10^{-5\cdot7}$	$1{\cdot}6 \times 10^{-14}$

The agreement between experiments at different concentrations is good, and gives a mean value $K = 2{\cdot}4 \times 10^{-14}$.

Titration in the Presence of Air.—A titration carried out in a closed vessel containing some air gave a precipitate, largely composed of ferric hydroxide, with some ferrosic hydroxide, at pH 5·25. The resultant curve (Curve 5, Fig. 1) resembles that obtained by Britton, and the apparent solubility product calculated from it is $5{\cdot}3 \times 10^{-39}$.

Ferrosic Hydroxide Precipitation.—The procedure described for ferrous hydroxide was used, with the addition of a measured quantity of 0·033M-ferric sulphate solution after reduction of the ferrous solution. In a typical experiment (Fig. 2), 15 ml. of 0·033M-Fe^{+++} and 50 ml. of 0·05M-Fe^{++} were titrated with 0·100N-NaOH. Basic ferric sulphate was first precipitated between pH 2·5 and 3·5, the curve (*A*—*B*) being of the characteristic type observed by Evans and Prior (*J.*, 1949, S 157). The complete precipitation of ferric iron was followed by further reaction of the precipitate with sodium hydroxide to form $Fe(OH)_3$, the pH rising rapidly during this process (*B*—*C*). At *C*, the formation of dark olive-green ferrosic hydroxide was accompanied by a sharp inflexion in the curve, and in the region *C*–*D*,

FIG. 2.



the pH readings dropped slowly after each addition of alkali, to the values shown. If the normally accepted formula for ferrosic hydroxide is assumed, the reaction in the region *C*–*D* is

$$2Fe(OH)_3 + Fe^{++} + 2OH' = Fe_3(OH)_8$$

and the solubility product of $Fe_3(OH)_8$ is therefore $K' = [Fe^{++}] \times [OH^-]^2$. The end point of this reaction was marked by an inflexion at *D*, after which the pH readings rose rapidly on to a curve *E*—*F* similar to those obtained with pure ferrous iron solutions.

Results were as follows:

Expt.	$[Fe^{++}]$ at *C*.	pH.	$[OH^-]$.		*K*.
1	$2{\cdot}38 \times 10^{-4}$	6·35	$10^{-7{\cdot}63}$		$5{\cdot}2 \times 10^{-15}$
2	$3{\cdot}20 \times 10^{-4}$	6·40	$10^{-7{\cdot}70}$		$8{\cdot}9 \times 10^{-15}$
3	$2{\cdot}35 \times 10^{-4}$	6·35	$10^{-7{\cdot}63}$		$5{\cdot}1 \times 10^{-15}$
				Mean	$6{\cdot}4 \times 10^{-15}$

Discussion.

Ferrous Hydroxide.—The value $2{\cdot}4 \times 10^{-14}$ for the solubility product is in good agreement with the results obtained by Bineau and by Whitman, from solubility determinations, and by Müller from the Fe^{+++}/Fe^{++} potential. The titration curves are variable in length, the molecular ratio of sodium hydroxide required to give complete precipitation being between 1·7 and 1·9. This is in agreement with the findings of Pickering (*J.*, 1907, **91**, 1981), who considered the precipitate to be $10FeO,SO_3$. The formation of such a compound is normally accompanied, however, by a clear inflexion at the end of precipitation, as in the case of $4CuO,SO_3$, or $5ZnO,SO_3$. In the case of ferrous iron the final inflexions are ill-defined, and in the last stages of the curve, the pH readings fall slowly when the solution is kept. This effect could result from the occlusion of ferrous sulphate on a precipitate of ferrous hydroxide, and the formation of a basic ferrous sulphate cannot therefore be inferred from this work.

Ferrosic Hydroxide.—The term " ferrosic hydroxide " has been applied to compounds with widely differing properties, and the value $6{\cdot}4 \times 10^{-15}$ for the solubility product applies only to the compound produced from mixed ferric and ferrous solutions under conditions of rising pH.

The addition of excess of alkali causes the formation of a black compound, insoluble in mineral acids, which has not been studied in detail. The rate of fall of pH in the later stages of the curve *C–D* was so slow that equilibrium was not always attained, and the length *C–D* has been found variable. In all cases, however, the length of this curve was considerably greater than that required for $Fe_2(OH)_3$, and corresponds with the formation of $Fe_4(OH)_{10}$ [in Fig. 2, Found: 11 ml., $Fe_2(OH)_3$ requires 5·0 ml. $Fe_4(OH)_{10}$ requires 10·0 ml.]. A compound corresponding to this formula was prepared by Baudisch and Merzer (*Biochem. Z.*, 1920, **37**, 107) who considered it to be HO·Fe·O·Fe(OH)$_2$. It appears that this compound is formed under the conditions of these experiments, by further reaction of $Fe_2(OH)_6$ in the presence of excess of ferrous iron.

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CHEMICAL RESEARCH LABORATORY, TEDDINGTON. [*Received, November 24th*, 1949.]

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180. *Aminoalkyl Tertiary Carbinols and Derived Products. Part II. 3-Amino-1 : 1-di-2′-thienyl-alkan-1-ols and -alk-1-enes.*

By D. W. ADAMSON.

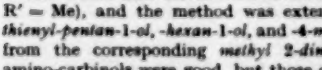
3-Amino- and *N*-substituted *3-amino-1 : 1-di-2′-thienylalkan-1-ols* (I) were prepared from 2-thienyl-lithium and 2-aminoalkanecarboxylates (II), obtained by addition of the appropriate amine to substituted acrylic esters. Substantial quantities of 2-β-piperidinopropionylthiophen (III), as well as the carbinol, were isolated in the Grignard reaction between 2-thienylmagnesium bromide and ethyl β-piperidinopropionate. The amino-carbinols were dehydrated to the *3-amino-* and *N*-substituted *3-amino-1 : 1-di-2′-thienylalk-1-enes* (IV).

Several amino-carbinols had high antispasmodic activity and a number of *NN*-disubstituted *3-amino-1 : 1-di-2′-thienylbut-1-enes* were potent analgesics.

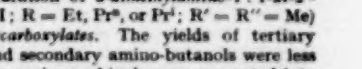
A NUMBER of the *N*-substituted 3-amino-1 : 1-diphenyl-propan-1-ols and -prop-1-enes described in Part I (*J.*, 1949, S 144) had interesting pharmacological properties (White, Fawcett, Green, and Hudson, to be published). The investigation of related compounds in which both phenyl groups of the parent compound are replaced by 2-thienyl groups, the synthesis of which is now described, forms part of our programme in this series.

Several *NN*-disubstituted *3-amino-1 : 1-di-2′-thienylpropan-1-ols* (I; R = H) were prepared by reaction of 2-thienyl-lithium with ethyl *NN*-disubstituted β-aminopropionates (II; R′ = H). *3-Amino-1 : 1-di-2′-thienylbutan-1-ol* (I; R = Me; R′ = R″ = H) and an extensive series of *N*-substituted derivatives were obtained similarly from the appropriate β-aminobutyrates (II; R′ = Me), and the method was extended to the preparation of *3-dimethylamino-1 : 1-di-2′-thienyl-pentan-1-ol, -hexan-1-ol*, and *-4-methylpentan-1-ol* (I; R = Et, Pr^n, or Pr^i; R′ = R″ = Me) from the corresponding *methyl 2-dimethylaminoalkanecarboxylates*. The yields of tertiary amino-carbinols were good, but those of the primary and secondary amino-butanols were less satisfactory (cf. Part I, *loc. cit.*) (Table II). The tertiary amino-carbinols were converted into water-soluble *hydrochlorides* or *hydrogen oxalates* and some into *methiodides*; the primary and secondary amino-carbinols gave neutral *oxalates*.

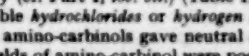
The yields of amino-carbinol were poor in the two examples in which the Grignard reaction was employed. Ethyl β-piperidinopropionate on reaction with 2-thienylmagnesium bromide (3 mols.) gave 2-β-piperidinopropionylthiophen (III) in 23% yield in addition to the expected *3-piperidino-1 : 1-di-2′-thienylpropan-1-ol* (I; R = H; NR′R″ = N<C$_5$H$_{10}$) in similar yield.



(I.)



(II.)



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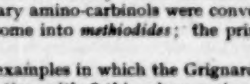

(IV.)

The formation of substantial amounts of ketone by the action of a Grignard reagent on an ester is usual but it has been recorded in a few instances in which the ester bears a tertiary amino-substituent, *e.g.*, the isolation of a small quantity of ketone from the reaction between ethyl β-piperidinopropionate and phenylmagnesium bromide was described in Part I (*loc. cit.*); Prelog and Hanonsek (*Chem. Abs.*, 1931, **25**, 4525) obtained 1-dimethylaminohexan-4-one as

well as 6-dimethylamino-3-ethylhexan-3-ol from ethylmagnesium bromide and ethyl γ-dimethylaminobutyrate; recently it has been claimed that ketones are formed exclusively from Grignard reagents and 4-carbalkoxy-4-phenyl-1-methylpiperidines (B.P. 614,567).

2-β-Piperidinopropionylthiophen (III) (also preparable by the Mannich reaction; Blicke and Burckhalter, *J. Amer. Chem. Soc.*, **1942**, **64**, 451) on further reaction with 2-thienylmagnesium bromide (3 mols.) gave the amino-carbinol in 31% yield. A similar reaction between 2-β-piperidinoisobutyrylthiophen and phenylmagnesium bromide to give 3-piperidino-1-phenyl-1-2′-thienyl-2-methylpropan-1-ol is described in B.P. Appl. 2255/47; Berger, Ziering, and Lee (*J. Org. Chem.*, **1946**, **12**, 904) describe the preparation of 4-hydroxy-4-2′-thienyl-1-butylpiperidine from 2-thienyl-lithium and 1-butyl-4-piperidone.

The 2-aminoalkane-carboxylic esters (II) (Table I) required as starting materials were conveniently prepared by addition of an amine to the appropriate substituted acrylic ester. This method has already been used for the preparation of a series of ethyl β-aminopropionates (Part I, *loc. cit.*) and of some ethyl β-aminobutyrates (Philippi and Spenner, *Monatsh.*, 1915, **36**, 97; Philippi and Galter, *ibid.*, 1929, **51**, 253; Morsch, *ibid.*, 1932, **60**, 50). The method has now been successfully applied to a series of methyl and ethyl β-aminobutyrates (II; R = Me, Et; R′ = Me) many of which are new, and to *methyl* and *ethyl* β-*dimethylamino*- and β-*piperidino-valerate* and -β-*methylvalerate* and the corresponding *hexoates* (II; R = Me, Et, R′ = Et, Pr^n, Pr^i, NR″R‴ = NMe_2, $N{<}C_5H_{10}$). Some of the higher homologues were unstable and decomposed when kept at room temperature for short periods.

Dehydration of the amino-carbinols furnished the corresponding 3-*amino*- and *N*-substituted 3-*amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes* (IV). The method of dehydration employed for the related diphenyl compounds (Part I, *loc. cit.*), namely, boiling under reflux in a mixture of acetic and hydrochloric acids, was successfully applied to the amino-propanols (I; R = H). The homologues (I; R = Me, Et, Pr^n, Pr^i), however, suffered considerable degradation with tar formation under these conditions, but warming with the mixed acids for a limited time on the steam-bath was usually satisfactory. In one example, dehydration was effected by warming in hydrochloric acid alone. 3-Amino-1 : 1-di-2′-thienylbut-1-ene, like the analogous diphenylallylamine (Part I, *loc. cit.*), was unstable, and it was necessary to employ milder conditions in its preparation from the amino-carbinol. The alkenylamines (Table III), which were purified by distillation under reduced pressure, were mobile liquids which became highly coloured on exposure to air; they were converted into water-soluble crystalline *hydrochlorides*, and some into *methiodides*.

The pharmacological properties of these compounds, which have been studied by Dr. A. C. White and Mr. A. F. Green of the Biological Division of these Laboratories, were of considerable interest. High antispasmodic activity was shown by several amino-carbinols, *e.g.*, the activity of (I; R = H, NR′R″ = $N{<}C_5H_{10}$) was favourable in relation to synthetic spasmolytics now in clinical use. The majority of the amino-carbinols were powerful local anæsthetics. A number of tertiary amino-butenes, in particular (IV; R = Me, NR′R″ = NMe_2, NEt_2, $N{<}C_4H_8$, $N{<}C_5H_{10}$), were potent analgesics, as active as morphine in the rat, with undesirable side-effects (in the dog) at a minimum; the alkenylamines (IV) in general also exhibited spasmolytic, antihistamine, and local anæsthetic activity. The detailed pharmacology will be reported elsewhere; a preliminary communication has been published (Adamson and Green, *Nature*, 1950, **165**, 122).

Our investigations in this series are being extended.

Experimental.

(M. p.s are uncorrected.)

2-Aminoalkanecarboxylic Esters (see Table I).—*β-Aminopropionates* (II; R′ = H). Ethyl β-dimethylamino-, β-diethylamino-, β-pyrrolidino-, and β-piperidino-propionates (II; R = Et, R′ = H, NR″R‴ = NMe_2, NEt_2, $N{<}C_4H_8$, $N{<}C_5H_{10}$) were prepared as described in Part I (*loc. cit.*).

β-Aminobutyrates (II; R′ = Me). Methyl or ethyl crotonate was added to the amine (1 mol.) under the various conditions described below, and the esters were isolated from the product by fractional distillation under reduced pressure. The results, and references to earlier syntheses, are summarised in Table I.

Method A. The primary amino-ester (II; R = Et, R′ = Me, R″ = R‴ = H) was prepared by mixing ethyl crotonate (100 g.) with ethanolic ammonia (400 c.c.; saturated at 15°) and heating in an autoclave for 7 hours at 105—110°.

Method B. The amine, dissolved in an equal volume of ethanol, was mixed with methyl or ethyl crotonate, and the product distilled after being kept for 14 days.

Method C. A mixture of the amine and ethyl crotonate was boiled under reflux for 3 hours.

Method D. In the preparation of *methyl β-pyrrolidinobutyrate* (II; R = R′ = Me, NR″R‴ = $N{<}C_4H_8$)

sufficient heat to cause boiling of the mixture was generated when pyrrolidine was mixed with methyl crotonate. The mixture was allowed to cool and was distilled after being kept overnight.

TABLE I.

2-Aminoalkane carboxylic esters, $CO_2R{\cdot}CH_2{\cdot}CHR'{\cdot}NR''R'''$.

				Yield,			Found, %			Required, %		
R.	R'.	NR''R'''.	Method.	%.	B. p. (mm.).	Formula.	C.	H.	N.	C.	H.	N.
Et	Me	NH_2	A	58	63—64° (12) [a]	—	—	—	—	—	—	—
,,	,,	NHMe	B	70	66—68 (12) [b]	—	—	—	—	—	—	—
,,	,,	NHEt	,,	78	77—79 (12) [c]	—	—	—	—	—	—	—
,,	,,	NHBu$^{\beta}$	,,	80	100 (17)	$C_{10}H_{21}O_2N$	63·4	10·7	7·5	64·2	11·2	7·5
,,	,,	,,	C	42	—	—	—	—	—	—	—	—
Me	,,	NMe_2	B	79	66 (17)	$C_7H_{15}O_2N$	57·5	10·0	9·4	57·9	10·3	9·7
Et	,,	,,	,,	75	178—180°	—	—	—	—	—	—	—
Me	,,	NEt_2	,,	57	84 (18)	$C_9H_{19}O_2N$	61·8	11·3	8·5	62·4	11·0	8·1
Et	,,	,,	,,	85	91—92 (18) [b]	—	—	—	—	—	—	—
Me	,,	NPr^{α}_2	,,	40	116—118 (15)	$C_{11}H_{23}O_2N$	66·0	11·5	7·1	65·7	11·4	7·0
,,	,,	NBu^{α}_2	,,	29	134—136 (15)	$C_{13}H_{27}O_2N$	68·1	11·8	6·4	68·1	11·8	6·1
Et	,,	NMe·CH_2Ph	C	41	156—158 (16)	$C_{14}H_{21}O_2N$	71·7	8·7	6·4	71·5	8·9	6·0
Me	,,	$N<C_4H_8$	D	89	100—102 (23)	$C_8H_{15}O_2N$	62·8	9·9	8·6	63·2	9·9	8·2
Et	,,	$N<C_5H_{10}$	C	85	110—114 (13) [d]	—	—	—	—	—	—	—
,,	,,	$N<(CH_2)_4>O$	,,	42	121—122 (12)	$C_{10}H_{19}O_3N$	59·3	9·2	7·3	59·7	9·5	7·0
Me	Et	NMe_2	E	50	76—80 (18)	$C_9H_{17}O_2N$	60·1	10·6	8·9	60·4	10·7	8·8
,,	,,	,,	F	83	—	—	—	—	—	—	—	—
Et	,,	,,	,,	85	88—90 (20)	$C_9H_{19}O_2N$	61·9	10·5	7·9	62·4	11·0	8·1
Me	,,	$N<C_5H_{10}$	E	65	122—123 (21)	$C_{11}H_{21}O_2N$	66·5	10·3	6·9	66·3	10·6	7·0
,,	,,	,,	F	76	—	—	—	—	—	—	—	—
Et	,,	,,	,,	73	130—132 (21)	$C_{12}H_{23}O_2N$ [e]	67·2	10·4	6·8	67·6	10·8	6·6
Me	Pr$^{\alpha}$	NMe_2	,,	74	90 (15)	$C_9H_{19}O_2N$	62·7	10·7	8·2	62·4	11·0	8·1
Et	,,	,,	,,	83	116—118 (24)	$C_{12}H_{23}O_2N$ [e]	64·3	10·7	7·3	64·2	11·2	7·5
Me	,,	$N<C_5H_{10}$	,,	69	140—141 (22)	$C_{12}H_{23}O_2N$ [e]	67·6	10·7	6·8	67·6	10·8	6·6
Et	,,	,,	,,	49	158—160 (30)	$C_{13}H_{25}O_2N$ [e]	—	—	—	—	—	—
Me	Pr$^{\beta}$	NMe_2	,,	69	86—88 (24)	$C_9H_{19}O_2N$	62·6	10·7	7·8	62·4	11·0	8·1
Et	,,	,,	,,	72	108—110 (25)	$C_{12}H_{23}O_2N$ [e]	—	—	—	—	—	—
Me	,,	$N<C_4H_{10}$	,,	29	130—133 (22)	$C_{12}H_{23}O_2N$ [e]	—	—	—	—	—	—
Et	,,	,,	,,	26	140—141 (17)	$C_{13}H_{25}O_2N$ [e]	—	—	—	—	—	—

[a] Philippi and Spenner, *Monatsh.*, 1915, **36**, 97. [b] Morsch, *Monatsh.*, 1932, **60**, 50. [c] Breckpot, *Bull. Soc. chim. Belg.*, 1923, **32**, 412. [d] Philippi and Galter, *Monatsh.*, 1929, **51**, 253.
[e] Decomposes on storage.

β-Amino-esters.—Higher homologues (II; R' = Et, Pr$^{\alpha}$, Pr$^{\beta}$). β-Ethyl-, β-n-propyl-, and β-isopropyl-acrylic acids were prepared by known methods (von Auwers, *Annalen*, 1923, **432**, 74) and were esterified with boiling methanol or ethanol and concentrated sulphuric acid. The methyl esters appear to be new: *methyl β-ethylacrylate*, b. p. 144—145° (Found: C, 63·1; H, 8·9. $C_6H_{10}O_2$ requires C, 63·2; H, 8·8%). *methyl β-n-propylacrylate*, b. p. 62—64°/22 mm. (Found: C, 65·7; H, 9·5. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%). *methyl β-isopropylacrylate*, b. p. 60—62°/22 mm. (Found: C, 65·4; H, 9·6%).

Methyl β-dimethylamino- and *β-piperidino-valerates* (II; R = Me, R' = Et, NR''R''' = NMe_2, $N<C_5H_{10}$) were prepared by mixing methyl β-ethylacrylate with the amine (1 mol.) in an equal volume of ethanol, and the product was distilled after 4 days (method E). Higher yields were obtained when 1·5 mols. of the amine were used (method F), and accordingly these conditions were employed in the preparation of *methyl* and *ethyl β-dimethylamino-* and *β-piperidino-valerates*, and -4-methylvalerates and the corresponding *hexoates* (II; R = Me, Et, R' = Et, Pr$^{\alpha}$, Pr$^{\beta}$, NR''R''' = NMe_2, $N<C_5H_{10}$).

Preparation of Amino-carbinols by Means of 2-Thienyl-lithium.—The 3-*amino-* and *N*-substituted 3-*amino*-1 : 1-*di*-2'-*thienylalkan*-1-*ols* (I) (Table II) were prepared from 2-thienyl-lithium and the appropriate β-amino-ester, the general method employed being illustrated by the example described below. As indicated in Table II, the preparation of three carbinols was repeated, with the difference that the 2-thienyl-lithium was prepared from *n*-butyl-lithium (Gilman and Shirley, *J. Amer. Chem. Soc.*, 1949, **71**, 1870); the yields were very similar to, and the products identical with, those obtained by the general method as given in the example.

3-*Dimethylamino*-1 : 1-*di*-2'-*thienylbutan*-1-*ol* (I; R = R' = R'' = Me). A slow stream of dry nitrogen was led into the apparatus throughout the reaction in order to maintain an inert atmosphere. Thiophen (50 g., 0·6 mol.) in ether (50 c.c.) was added to an ethereal solution of phenyl-lithium prepared from bromobenzene (94 g., 0·6 mol.), lithium (8·5 g., 1·2 atoms), and ether (400 c.c.), and the mixture boiled under reflux for 2 hours. Ethyl β-dimethylaminobutyrate (32·0 g., 0·2 mol.) in ether (50 c.c.) was then added gradually to the mixture, stirred and cooled at −20°. Stirring was continued for 1 hour at room temperature and the mixture, from which a fawn-coloured solid had separated, was kept overnight. Ice (100 g.) was added with stirring, followed by glacial acetic acid until the solution was acidic to litmus. The crude amino-carbinol hydrobromide which separated as a brown crystalline solid was filtered off and washed with ether. The salt was suspended in chloroform, excess of ammonia added with shaking, the chloroform layer separated, washed with water, and dried (Na_2SO_4), and the chloroform evaporated. The residual dark brown oil (46 g.) rapidly crystallised; it was dissolved in boiling light petroleum (500 c.c.; b. p. 40—60°), and the solution filtered from black amorphous material and evaporated to *ca.* 120 c.c. The amino-carbinol crystallised on cooling and had m. p. 85—88° (40 g., 71% yield). Recrystallisation from ethanol gave 36 g., m. p. 90—91°, unchanged by further crystallisations.

TABLE II.

3-*Amino*-1 : 1-*di*-2'-*thienylalkan*-1-*ols*. [ ]$_2$C(OH)·CH$_2$·CHR·NR'R''.

					Found, %.					Required, %.				
R.	NR'R''.	Yield, %	M. p.†	Formula †	C.	H.	N.	S.	Cl or I.	C.	H.	N.	S.	Cl or I.
H	NMe_2	72*	126—137°	$C_{16}H_{19}ONS_2$	58·4	6·4	5·0	23·8	—	58·5	6·4	5·2	24·0	—
,,	,,		170—171 *	$C_{16}H_{19}ONS_2,C_2H_2O_4$	50·6	5·5	—	—	—	50·4	5·3	—	—	—
,,	,,	18*	65	$C_{16}H_{19}ONS_2$	60·9	7·2	4·6	21·3	—	61·0	7·1	4·7	21·7	—
,,	,,		196—197 *	$C_{16}H_{19}ONS_2$,HCl	—	—	—	19·0	10·9	—	—	—	19·3	10·7
,,	,,		193—194 *	$C_{16}H_{19}ONS_2I$	—	—	—	14·7	28·9	—	—	—	14·6	29·1
,,	$N<C_4H_8$	73	118—119	$C_{18}H_{21}ONS_2$	61·5	6·2	4·6	21·6	—	61·4	6·5	4·8	21·8	—
,,	,,		196—197 *	$C_{18}H_{21}ONS_2$,HCl	—	—	—	19·3	10·8	—	—	—	19·4	10·8
,,	,,		179—180 *	$C_{18}H_{21}ONS_2I$	—	—	—	14·3	29·4	—	—	—	14·7	29·2
,,	$N<C_5H_{10}$	66	70—72	$C_{19}H_{23}ONS_2$	62·7	6·8	4·8	21·0	—	62·5	6·8	4·6	20·8	—
			(b. p. 176—180/0·04 mm.)											
			198 *	$C_{19}H_{23}ONS_2$,HCl	—	—	—	—	10·4	—	—	—	—	10·3
			188—189 *	$C_{19}H_{23}ONS_2I$	—	—	—	14·1	28·1	—	—	—	14·3	28·3
Me	NH_2	34	126—127	$C_{15}H_{17}ONS_2$	56·9	6·1	5·3	25·0	—	56·9	5·9	5·5	25·3	—
,,	NHEt	24	151—152 *	$C_{15}H_{17}ONS_2,\frac{1}{2}C_2H_2O_4$	52·1	5·3	—	—	—	52·4	5·4	—	—	—
			80—81	$C_{17}H_{21}ONS_2$	60·3	6·6	4·9	22·6	—	59·8	6·8	5·0	22·8	—
			(b. p. 139—143/0·1 mm.)											
			204—205 *	$C_{17}H_{21}ONS_2,\frac{1}{2}C_2H_2O_4$	55·6	6·2	—	—	—	55·2	6·1	—	—	—
,,	NHBu	40	63—64	$C_{19}H_{25}ONS_2$	62·4	7·3	4·7	21·1	—	62·1	7·4	4·5	20·7	—
,,	,,		183—184 *	$C_{19}H_{25}ONS_2,\frac{1}{2}C_2H_2O_4$	57·5	6·8	—	—	—	57·6	6·8	—	—	—
,,	NMe_2	71	90—91	$C_{16}H_{19}ONS_2$	60·1	6·9	4·8	22·7	—	59·8	6·8	5·0	22·8	—
,,	,,		198—199 *	$C_{16}H_{19}ONS_2$,HCl	—	—	—	—	11·3	—	—	—	—	11·2
,,	,,		189 *	$C_{16}H_{19}ONS_2I$	—	—	—	—	29·8	—	—	—	—	30·0
,,	NEt_2	79	75—76	$C_{17}H_{21}ONS_2$	62·1	7·3	4·4	21·1	—	62·1	7·4	4·5	20·7	—
			117—118	$C_{17}H_{21}ONS_2,C_2H_2O_4$	54·5	6·3	—	—	—	54·1	6·3	—	—	—
,,	NPr^n_2	70	91—92	$C_{19}H_{25}ONS_2$	64·0	8·0	4·2	18·9	—	64·1	8·0	4·2	19·0	—
			100	$C_{19}H_{25}ONS_2,C_2H_2O_4$	56·2	6·7	—	—	—	56·2	6·8	—	—	—
,,	NMe·CH_2Ph	56	73—74	$C_{20}H_{21}ONS_2$	67·6	6·2	3·9	17·6	—	67·2	6·4	3·9	17·9	—
			143—144 *	$C_{20}H_{21}ONS_2,C_2H_2O_4$	59·3	5·7	—	—	—	59·1	5·6	—	—	—
,,	$N<C_4H_8$	77	88—89	$C_{16}H_{21}ONS_2$	62·8	7·0	4·6	20·9	—	62·5	6·8	4·6	20·9	—
			172—173 *	$C_{16}H_{21}ONS_2,C_2H_2O_4$	54·3	5·9	—	16·0	—	54·4	5·8	—	16·1	—
,,	$N<C_5H_{10}$	55*	82—83	$C_{17}H_{23}ONS_2$	63·6	7·2	4·5	19·6	—	63·6	7·2	4·4	19·9	—
			(b. p. 146—148/0·02 mm.)											
			166—167 *	$C_{19}H_{23}ONS_2,C_2H_2O_4$	55·6	6·2	—	—	—	55·5	6·1	—	—	—
,,	$N<[CH_2]_2>O$	48	105—106	$C_{16}H_{21}O_2NS_2$	59·4	6·4	4·3	19·8	—	59·4	6·5	4·3	19·8	—
			134—135 *	$C_{16}H_{21}O_2NS_2,C_2H_2O_4$	52·7	5·9	—	—	—	52·3	5·6	—	—	—
Et	NMe_2	73*	83—84	$C_{16}H_{21}ONS_2$	61·0	7·1	4·7	21·3	—	61·0	7·1	4·7	21·7	—
			170—171 *	$C_{16}H_{21}ONS_2,C_2H_2O_4$	53·1	5·9	—	—	—	53·0	6·0	—	—	—
Pr^n	,,	43	—	$C_{18}H_{25}ONS_2$	62·4	7·1	4·4	20·8	—	62·1	7·4	4·5	20·7	—
			(b. p. 145—147/0·05 mm.)											
			138—139 *	$C_{18}H_{25}ONS_2,C_2H_2O_4$	54·3	6·3	—	—	—	54·1	6·3	—	—	—
Pr^i	,,	71	56—57	$C_{18}H_{25}ONS_2$	62·2	7·1	4·5	20·8	—	62·1	7·4	4·5	20·7	—
			125—126	$C_{18}H_{25}ONS_2,C_2H_2O_4$	54·2	6·1	—	15·9	—	54·1	6·3	—	16·0	—

* 2-Thienyl-lithium prepared from *n*-butyl-lithium. * Prepared by the Grignard reaction.
* M. p. with decomposition. † The m. p. and formula of the base are given first, followed by those of its derivatives.

Preparation of Amino-carbinols by the Grignard Reaction.—**3-Piperidino-1 : 1-di-2′-thienylpropan-1-ol** (I; R = H, NR′R″ = N<C$_5$H$_{10}$). Ethyl β-piperidinopropionate (37 g., 0·2 mol.) in ether (50 c.c.) was added gradually to an ethereal solution of the Grignard reagent made from 2-bromothiophen (98 g., 0·6 mol.) and magnesium (14·6 g., 0·6 atom) in ether (50 c.c.), stirred and cooled in a bath at 0°. The mixture, from which a heavy oil had separated, was boiled under reflux for 3 hours and kept overnight at room temperature. Crushed ice (100 g.) was added, followed by aqueous ammonium chloride (25%; 100 c.c.). Acetic acid was then added gradually with stirring until the solution was acid to litmus, and the cream-coloured solid which separated was filtered off and washed with ether. The solid was dissolved in chloroform and shaken with excess of ammonia; the chloroform layer was washed with water and dried (Na_2SO_4), and the chloroform evaporated. The residual brown mobile oil was distilled at 0·1 mm. pressure and the following fractions collected: (i) b. p. <160°, 16·5 g., (ii) b. p. 160—188°, 2·0 g., (iii) b. p. 188—194°, 15·3 g., and (iv) b. p. >194°, approx. 10 g. (resinous). Fraction (iii) which rapidly crystallised was the amino-carbinol, m. p. 70—72° after recrystallisation from ethanol (yield 24%). Redistillation of fraction (i) gave, besides some low-boiling material, a mobile liquid, b. p. 102—105°/0·03 mm. (10·1 g., 23%), which was identified as 2-β-piperidinopropionylthiophen (III) [hydrochloride (recrystallised from methanol), m. p. 203—205°, not depressed by a specimen prepared by the Mannich reaction (Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 451)].

TABLE III.

3-*Amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes*. $\left[\text{C}_4\text{H}_3\text{S}\right]_2\text{C:CH·CHR·NR′R″}$

		Base.	Hydrochloride.					
						Found, %		Reqd., %
R.	NR′R″.	B. p. (mm.).	M. p.	Formula.	Cl.	S.	Cl.	S.
H	NMe_2	91—94° (0·05)	144—145°	$C_{12}H_{12}NS_2$,HCl	12·5	22·7	12·4	22·4
,,	NEt_2	—	116—117	$C_{14}H_{16}NS_2$,HCl	11·5	19·8	11·3	20·4
,,	N<C_5H_4	—	102—103	$C_{15}H_{13}NS_2$,HCl	11·3	20·3	11·4	20·5
,,	N<C_5H_{10}	143 (0·05) [a]	171—173 [a]	$C_{16}H_{18}NS_2$,HCl	10·9	19·8	10·9	19·7
Me	NH_2	—	174—175 [a]	$C_{12}H_{12}NS_2$,HCl	12·6	23·2	13·1	23·2
,,	NHEt	112—114 (0·03)	134—135	$C_{14}H_{17}NS_2$,HCl	11·9	21·3	11·8	21·4
,,	NHBu	122—124 (0·04) [b]	123—124	$C_{16}H_{21}NS_2$,HCl	11·2	19·8	10·8	19·5
,,	NMe_2	123—125 (0·05)	169—170	$C_{14}H_{15}NS_2$,HCl	12·1	22·0	11·8	21·4
,,	NEt_2	122—128 (0·03)	152—153	$C_{16}H_{21}NS_2$,HCl	10·6	19·5	10·8	19·5
,,	NPr^n_2	119—121 (0·01)	112—115°	$C_{18}H_{25}NS_2$,HCl	10·0	17·8	10·0	18·0
,,	NMe·CH_2Ph	146—148 (0·01)	160—161 [a]	$C_{20}H_{21}NS_2$,HCl	9·6	16·3	9·5	17·0
,,	N<C_5H_4	132—135 (0·1)	167—169	$C_{19}H_{19}NS_2$,HCl	10·9	19·5	10·9	19·7
,,	N<C_5H_{10}	132—136 (0·05)	188—189	$C_{17}H_{21}NS_2$,HCl	10·5	18·6	10·5	18·9
,,	N<[CH_2]$_4$>O	130—136 (0·05)	181—182	$C_{16}H_{19}ONS_2$,HCl	10·4	18·4	10·4	18·7
Et	NMe_2	110—112 (0·03)	138—139	$C_{14}H_{15}NS_2$,HCl	11·5	20·3	11·3	20·4
Pr^n	,,	116—118 (0·03)	158—159	$C_{15}H_{21}NS_2$,HCl	10·8	19·6	10·8	19·5
Pr^i	,,	107—109 (0·03) [c]	(159—160 [a]) [c]	—	—	—	—	—

[a] Found: C, 66·7; H, 6·4; N, 4·7; S, 22·4. $C_{14}H_{19}NS_2$ requires C, 66·4; H, 6·6; N, 4·8; S, 22·2%. [b] Found: C, 66·0; H, 7·2; N, 4·8; S, 22·0. $C_{16}H_{21}NS_2$ requires C, 66·0; H, 7·2; N, 4·8; S, 22·0%. [c] Found, for hydrate: H_2O, 2·3. $C_{15}H_{21}NS_2$,HCl,$\frac{1}{2}H_2O$ requires H_2O, 2·5%. [d] Found: C, 66·0; H, 7·3; N, 4·8; S, 22·0. $C_{14}H_{21}NS_2$ requires C, 66·0; H, 7·2; N, 4·8; S, 22·0%. [e] Found, for hydrogen oxalate: S, 16·7. $C_{14}H_{21}NS_2,C_2H_2O_4$ requires S, 16·8%.

[a] M. p. with decomposition.

The amino-carbinol was also prepared from 2-β-piperidinopropionylthiophen hydrochloride (0·1 mol.) and 2-thienylmagnesium bromide (0·3 mol.) under conditions similar to those described above, a yield of 31% being obtained.

3-*Diethylamino*-1 : 1-*di*-2′-*thienylpropan*-1-*ol* (I; R = H, R′ = R″ = Et). The amino-carbinol was obtained in 18% yield from the reaction between 2-thienyl-lithium (0·3 mol.) and ethyl β-diethylamino-propionate (0·1 mol.) under conditions similar to those described above for the piperidino-analogue. In this example also a considerable quantity of a low-boiling fraction was obtained when the crude product was distilled under reduced pressure, but on redistillation it boiled over a wide range with some decomposition.

The amino-carbinols were purified by recrystallisation from ethanol; in those examples for which a b. p. is recorded in Table II, the crude products were given a preliminary purification by fractional distillation under reduced pressure.

The *hydrochlorides* were prepared by passing dry hydrogen chloride into a solution of the base in chloroform at 0° until neutrality was reached. The salts crystallised on the addition of ether and were recrystallised from ethanol.

The oxalates were prepared by mixing the base (1 mol.) in ethanol with anhydrous oxalic acid (1 mol.) in ethanol at room temperature. The salts which rapidly separated were recrystallised from ethanol. Under these conditions the primary and secondary amino-carbinols gave neutral *oxalates*, and the tertiary amines *hydrogen oxalates*.

The *methiodides* were prepared by adding methyl iodide (2 mols.) to a solution of the tertiary amino-carbinols in a small volume of acetone. After several hours, the salts which had separated were recrystallised from methanol.

Dehydration of Amino-carbinols.—The method described for the dehydration of the related diphenyl-carbinols (Part I, *loc. cit.*) was successfully applied to the aminopropanols (I; R = H), the yields of

distilled allylamine being approx. 70% (example 1). When this method was applied to some amino-butanols (I; R = Me), however, extensive degradation occurred and black amorphous solids were formed (example 2). The amino-butanols and higher homologues were therefore dehydrated under milder conditions, whereby the unsaturated amines were obtained usually in yields of 70—90% (example 3). In the preparation of **3-*benzylmethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene*** (IV; R = R′ = Me, R″ = CH_2Ph) by this method considerable quantities of tar were produced, and the yield was 40%. 3-Amino-1 : 1-di-2′-thienylbutan-1-ol (I; R = Me, R′ = R″ = H) was completely decomposed to tarry products by this method, and therefore dehydration was effected under milder conditions as described in example 4. Dehydration by warming of the carbinol with hydrochloric acid alone was successful in the preparation of **3-*diethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene*** (IV; R = Me, R′ = R″ = Et) (example 5).

Example 1. 3-Dimethylamino-1 : 1-di-2′-thienylpropan-1-ol (15 g.) was dissolved in a mixture of concentrated hydrochloric acid (30 c.c.) and glacial acetic acid (100 c.c.), and the solution boiled under reflux for 20 minutes. The deeply coloured solution was then concentrated under reduced pressure, the residue treated with excess of ammonia, and the base extracted with ether. The ethereal solution was dried (Na_2SO_4), the ether evaporated, and the residue distilled under reduced pressure. The product, **3-*dimethylamino*-1 : 1-*di*-2′-*thienylprop*-1-*ene*** (IV; R = H, R′ = R″ = Me), was a colourless mobile liquid which became purple on exposure to air and had b. p. 91—94°/0·05 mm. (yield 9·9 g., 71%).

Example 2. 3-Dimethylamino-1 : 1-di-2′-thienylbutan-1-ol (15 g.) was boiled under reflux in acidic solution as described in example 1. A black solid was deposited on the walls of the flask. The mixture was concentrated under reduced pressure and filtered. The residue was a black intractable solid (melting between 135° and 180°), insoluble in boiling water or aqueous mineral acids; the dark filtrate gave a small amount of tarry material when basified.

Example 3. 3-Piperidino-1 : 1-di-2′-thienylbutan-1-ol (20 g.) was warmed on the steam-bath for 15 minutes with concentrated hydrochloric acid (40 c.c.) and glacial acetic acid (130 c.c.). The solution was worked up as described in example 1 (care being taken to keep the temperature low during the concentration of the solution), and the product, **3-*piperidino*-1 : 1-*di*-2′-*thienylbut*-1-*ene*** (IV; R = Me, NR′R″ = N·C_5H_{10}), was distilled under reduced pressure, having b. p. 132—136°/0·05 mm. (yield 14·5 g., 78%).

Example 4. Dry hydrogen chloride was led into a cooled solution of 3-amino-1 : 1-di-2′-thienylbutan-1-ol (1·6 g.) in chloroform (8 c.c.). The white solid which separated quickly dissolved, the solution became pale brown, and drops of water separated. The chloroform solution was dried (Na_2SO_4) and evaporated under reduced pressure to small volume, and ether added gradually until crystallisation commenced. **3-*Amino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* *hydrochloride*** (IV; R = Me, R′ = R″ = H) was obtained as fawn-coloured crystals, m. p. 174—175° (decomp.).

Example 5. 3-Diethylamino-1 : 1-di-2′-thienylbutan-1-ol (15 g.) was added to hydrochloric acid (6*N*.; 75 c.c.), and the mixture heated on the steam-bath for 15 minutes. The resulting deeply coloured solution was cooled, excess of ammonia added, and the base extracted with chloroform. The chloroform was evaporated, and the residual oil distilled under reduced pressure to give **3-*diethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene*** (IV; R = Me, R′ = R″ = Et), b. p. 122—128°/0·03 mm. (10·5 g., 74%).

The **3-*amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes*** and their ***hydrochlorides*** are recorded in Table III. The hydrochlorides, prepared in a similar manner to those of the amino-carbinols, were recrystallised from ethanol–ethyl acetate. In some cases the hydrochlorides were also isolated directly from the dehydration mixture by evaporation to dryness and recrystallisation of the solid residue.

The following methiodides were prepared by mixing the base with excess of methyl iodide in acetone solution. After several hours, the product was filtered off and recrystallised from methanol. **3-*Diethylamino*-1 : 1-*di*-2′-*thienylprop*-1-*ene* *methiodide***, m. p. 174—175° (decomp.) (Found: I, 31·0. $C_{14}H_{22}NIS_2$ requires I, 30·3%); **3-*pyrrolidino*-1 : 1-*di*-2′-*thienylprop*-1-*ene* *methiodide***, m. p. 186° (decomp.) (Found: I, 30·0. $C_{14}H_{20}NIS_2$ requires I, 30·5%); **3-*piperidino*-1 : 1-*di*-2′-*thienylprop*-1-*ene* *methiodide***, m. p. 193—194° (decomp.) (Found: I, 29·3. $C_{15}H_{22}NIS_2$ requires I, 29·5%); **3-*dimethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* *methiodide***, decomposes from 130° (Found: I, 32·3. $C_{14}H_{22}NIS_2$ requires I, 31·4%).

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CHEMICAL DIVISION, WELLCOME RESEARCH LABORATORIES,
BECKENHAM, KENT.

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181. *Reactions of Ethylene Oxides. Part IV. The Reaction of Epichlorohydrin with Some Aromatic Amines.*

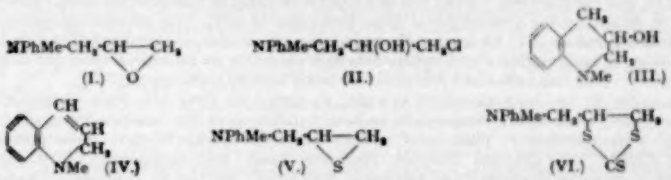
By W. DAVIES and W. E. SAVIGE.

Epichlorohydrin with one mole or two moles of methylaniline gives good yields of 1-chloro-3-*N*-methylanilinopropan-2-ol (II) and 1 : 3-di-(*N*-methylanilino)propan-2-ol, respectively. Modification of the conditions brings about the production of dimethylaniline, 1-methyltetrahydroquinoline, and 3-hydroxy-1-methyltetrahydroquinoline (which readily loses water to form 1-methyl-1 : 2-dihydroquinoline). The basic group in the oxide derived from the chlorohydrin (II) has little effect on its general properties and reactions, which are essentially those of a normal $\alpha\beta$-oxide.

REACTION of methylaniline and epichlorohydrin, described chiefly in the patent literature, has been reinvestigated in order to prepare, and examine the properties of, a compound such as

3-*N*-methylanilinopropylene oxide (I) containing a basic centre separated by one methylene group from an aβ-oxide ring. The reaction is found to give a variety of products depending on the experimental conditions. For example, Eisleb (D.R.-P. 473,219/1929; U.S.P. 1,790,042/1931) obtained (I) by interaction of equimolar quantities of epichlorohydrin and methylaniline in aqueous alcohol, followed by treatment with alkali. On the other hand, Lange (D.R.-P. 619,825) obtained 3-hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline (III) when the reaction was carried out in chlorobenzene. It is now found that in hot aqueous alcohol or in boiling xylene the chief product is 1-*chloro*-3-*N*-*methylanilinopropan*-2-*ol* (II), which is converted by alkali into the oxide (I).

Further differences are found when the condensation occurs in the absence of solvent and when the temperature is varied. 1 : 3-Di-(*N*-methylanilino)propan-2-ol was the only pure compound isolated, and that in very small yield, by Wedekind and Bruch (*Annalen*, 1929, **471**, 94) from equimolar amounts of reactants without a solvent, on the water-bath. This diamine is now found to be produced almost quantitatively from two moles of methylaniline at rather higher temperatures, a process which recalls the formation of 1 : 3-dianilinopropan-2-ol from epichlorohydrin and aniline (Fouconnier, *Compt. rend.*, 1888, **107**, 250; Fukagawa, *Ber.*, 1935, **68**, *B*, 1344).



However, if equimolar amounts of the reactants are refluxed without a solvent for a short time, the reaction becomes violently exothermic, and the products, after treatment with concentrated alkali, are dimethylaniline, kairoline (1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline), and 3-hydroxykairoline (III) in yields of 8, 10, and 45% respectively, the remainder consisting of small intermediate fractions and higher-boiling material. If the subsequent alkali treatment is omitted, it is very difficult to separate 3-hydroxykairoline by distillation from the chlorohydrin (II) present in the reaction mixture. When the conditions of the reaction are more controlled, dimethylaniline, the oxide (I), 3-hydroxykairoline (III), and 1 : 3-di-(*N*-methylanilino)propan-2-ol are isolated in yields of 2, 35, 10, and 2% respectively. The kairoline obtained is identified in the usual way. Little information is given by Lange (*loc. cit.*) about the main heterocyclic product 3-hydroxykairoline. It has the high viscosity and boiling point characteristic of tertiary ethanolamine derivatives, and the presence of the hydroxy-group is shown by reaction with methylmagnesium iodide and phenyl *iso*cyanate. The position of the hydroxy-group has not been proved, but the 3-position is to be expected if the nitrogen ring is formed by intramolecular reaction of either (I) or (II). Similarly, 3-hydroxy-1-phenyl-1 : 2 : 3 : 4-tetrahydroquinoline is considered (D.R.-P. 284,291) to be the product from the reaction of epichlorohydrin and diphenylamine under pressure, which, if catalysed by sodium iodide, is now found to occur at ordinary pressure; the presence of the hydroxy-group is shown by the formation of a crystalline *phenylurethane*.

3-Hydroxykairoline is converted by distillation over solid potassium hydroxide into a lower-boiling liquid, 1-*methyl*-1 : 2-*dihydroquinoline* (IV), readily reduced to kairoline by zinc and sulphuric acid. This dihydro-compound, like 1-methyl-2-propyl-1 : 2-dihydroquinoline (von Braun and Aust, *Ber.*, 1914, **47**, 3023), polymerises readily when kept, thus favouring the 1 : 2- rather than the 1 : 4-dihydro-structure.

The mechanism of the production of 3-hydroxykairoline (III) is deduced from known reactions of epichlorohydrin. Thus, in the presence of hydroxylic solvents or at high temperatures, epichlorohydrin generally combines with amines to form first the 1-chloropropan-2-ol, and it has now been confirmed that with an equimolecular quantity of *p*-toluidine it gives the crystalline *p*-tolyl analogue of (II) (Cohn and Friedlander, *Ber.*, 1904, **37**, 3034); Drefus (F.P. 702,553) claims a similar preparation of the α-naphthyl analogue. Lange (U.S.P. 2,150,001/1939) also reports that primary aromatic amines can yield tertiary amines of the type $Ar{\cdot}N[CH_2{\cdot}CH(OH){\cdot}CH_2Cl]_2$. Thus, methylaniline probably produces initially (II) which then cyclises to (III) with loss of hydrogen chloride. This view is supported by the decomposition

of (II) at 180—200°, to give 50% of (III) together with dimethylaniline and a polymer. A similar ring closure is involved in the formation of lilolidine by heating 1-3′-chloropropyldihydroindole (von Braun, Heider, and Wyczatkowska, *Ber.*, **1918**, **51**, 1219), and in the mechanism postulated by Lange (I.G. Farbenind., Zetco Reports, Jan., 1946, F.I.A.T. Microfilm Reel C 60, PB L 64079) for the production of 3-hydroxytetrahydroquinoline derivatives from epichlorohydrin and α- or β-naphthylamine or secondary arylalkylamines. Further analogous reactions involving primary and secondary aromatic amines are set out by Lange and Heiberger (D.R.-P. 634,038) and Lange (U.S.P. 2,194,399/1940).

The condensation of methylaniline or similar amines with epichlorohydrin to produce kairoline (or analogous bases) and dimethylaniline (or similar amines) is apparently novel, and the mechanism is not yet clearly understood. Dunlop and Jones (*J.*, 1909, **95**, 420) showed that methylaniline was converted into dimethylaniline by methyl bromide which is produced when ethylene dibromide and methylaniline form 1 : 4-diphenylpiperazine. (For similar fissions of alkyl groups attached to nitrogen see Wedekind and Bruch, *loc. cit.*, p. 76, and Thorpe and Wood, *J.*, 1913, **103**, 1611.) The somewhat analogous conversion of methylaniline into dimethylaniline may occur *via* methyl chloride during the condensation with epichlorohydrin, but it is probable that an intermediate compound (*e.g.*, II) undergoes fission at the link between the N·CH_3 and the CH(OH). That this link can be unstable in halogen-free compounds related to (II) is shown by the production of dimethylaniline in 50% yield on decomposition of the crude *trithiocarbonate* (VI) by heat. Moreover, the production of dimethylaniline during the inter-action of methylaniline and epichlorohydrin seems to be associated with the formation of kairoline. This and associated reactions are being further investigated.

The oxide (I) has been examined in order to verify its structure, since condensations of epichlorohydrin with certain reagents have been found to give the unsaturated alcohol rather than the expected oxide. Thus, with sodium acetylide epichlorohydrin gives pent-2-en-4-yn-1-ol, $CH{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$ (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1610) and with sodium sulphinates gives sulphones $R{\cdot}SO_2{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$ (Culvenor, Davies, and Savige, *J.*, 1949, 2200) which are also formed by the action of cold dilute alkali on the chloroalcohols, $R{\cdot}SO_2{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2Cl$. The dioxan type of dimer from the unsaturated alcohol is also sometimes formed, but that possibility is discarded in the case of the methylaniline product, because the latter has great chemical activity and a low boiling point. The following reactions of (I) are characteristic of αβ-oxides, and are unlikely to occur readily with the unsaturated alcohol, NPhMe·$CH{=}CH{\cdot}CH_2{\cdot}OH$ unless its double bond is far more reactive than the formula indicates.

Methylaniline gives with (I) the expected crystalline diamine 1 : 3-di-(*N*-methylanilino)-propan-2-ol; Eisleb (*loc. cit.*; also U.S.P. 1,845,403/1932) obtained analogous products from (I) with ammonia and with ethylamine. The oxide (I) is converted by dilute sulphuric acid into the crystalline *glycol*, NPhMe·$CH_2CH(OH){\cdot}CH_2{\cdot}OH$, by sodium sulphite into an *isethionate*, probably NPhMe·$CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}SO_3Na$, and by thiourea into the corresponding *sulphide* (V). Potassium methyl xanthate (cf. Culvenor, Davies, and Pausacker, *J.*, 1946, 1051) with (I) forms the corresponding impure trithiocarbonate (VI) characterised as its *picrate*. Finally, the absence of active hydrogen was shown by failure to react with methylmagnesium iodide, and absence of a hydroxy-group by infra-red analysis, indicating that the compound is the oxide (I) and not the unsaturated alcohol.

It is to be expected that salt formation involving the nitrogen in (I) would favour the formation of the unsaturated alcohol, but it has not been possible to obtain a crystalline methyl iodide derivative of (I), and dry hydrogen chloride at 0° yields an oily hydrochloride which cannot be purified and readily isomerises on warming to give a chlorohydrin, probably (II). However, the corresponding sulphide (V) does give a crystalline *monomethiodide*, which is regarded as an ammonium and not a sulphonium salt (cf. Culvenor, Davies, and Heath, *J.*, 1949, 282) and shows evidence of the retention of the thiairene ring. The properties of αβ-oxides containing an electrophilic group are being further studied.

Experimental.

Interaction of Epichlorohydrin with Methylaniline.—1-*Chloro*-3-N-*methylanilinopropan*-2-*ol* (II), a pale yellow viscous liquid, b. p. 132—134°/0·8 mm., 140°/2·5 mm., n_D^{20} 1·572, was obtained when epichlorohydrin (25 ml., 0·32 mol.), methylaniline (25 ml., 0·23 mol.), water (20 ml.), and alcohol (30 ml.) were heated under reflux for 2 hours and then treated with water (20 ml.), the product being extracted with ether, dried, and distilled (Found: C, 61·3, 61·25; H, 7·2, 7·0; N, 7·4. $C_{10}H_{14}ONCl$ requires C, 60·2; H, 7·0; N, 7·0%). The high values for carbon and nitrogen are attributed to slight contamination of the product with 3-hydroxykairoline (III) into which (II) was partly converted at the temperature of distillation. When (II) was redistilled at 167°/15 mm., sufficient (III) was produced to be identified

as its methiodide, and the last few viscous drops of the distillate gave the blue coloration in air and other reactions indicative of the presence of dimethylaniline hydrochloride. The chlorohydrin (II), b. p. 152—155°/4·5 mm., was also obtained on refluxing epichlorohydrin (18 ml.) and methylaniline (22 ml.) in xylene (35 ml.) for 6 hours, the product being again contaminated with (III), but no reaction occurred in boiling acetone with or without potassium iodide. Methylmagnesium iodide gave methane by interaction with (II), which yielded no crystalline derivative with picric or picrolonic acid, phenyl isocyanate, methyl iodide, or dry hydrogen chloride.

1 : 3-Di-(*N*-methylanilino)propan-2-ol, b. p. 195—198°/0·25 mm., m. p. 80°, short needles from benzene–light petroleum (Found : C, 76·4; H, 8·25; N, 10·15. Calc. for $C_{17}H_{22}ON_2$: C, 75·6; H, 8·15; N, 10·4%), previously made by Wedekind and Bruch (*loc. cit.*, who record m. p. 82°, b. p. 180—240°/20 mm.), was formed almost quantitatively from methylaniline (2·5 g.) and epichlorohydrin (0·9 g.) at 155° (1 hour) and then 170° (1 hour), the viscous acid product being then dissolved in dilute hydrochloric acid (5 ml.) and treated with aqueous sodium hydroxide.

In the absence of solvents, equimolecular amounts of methylaniline and epichlorohydrin gave 1-methyltetrahydroquinoline derivatives, the formation of which was favoured by high temperatures. Residual viscous material was also produced, and this can be the main product if the temperature of the reaction is too high. The following are typical condensations. (i) Epichlorohydrin (34·8 ml.) was heated under reflux, and methylaniline (43·6 ml.) added in small portions during ½ hour. Five minutes later, an exothermic reaction occurred, the temperature rising to >200°. The mixture was warmed on the water-bath for a further hour, cooled, and stirred with ether and a solution of sodium hydroxide (25 g.) in water (50 ml.) for 1 hour. The dried ethereal extract gave, after two refractionations, the following chlorine-free fractions, together with unchanged epichlorohydrin (5 ml.) and a viscous residue (20 ml.) : (*a*) b. p. 74—77°/13 mm. (6 ml.), identified by its picrate as dimethylaniline; (*b*) b. p. 62°/0·15 mm., 243°/756 mm., n_D^{25} 1·585 (8 ml.), kairoline (Found : C, 81·65; H, 9·0; N, 9·7. Calc. for $C_{10}H_{11}N$: C, 81·65; H, 8·85; N, 9·5%), a mobile liquid insoluble in water; and (*c*) b. p. 134—136°/0·18 mm., 290°/760 mm., n_D^{25} 1·595 (35 ml.), 3-hydroxykairoline (III), an extremely viscous liquid for which Lange (D.R.-P. 619,825) gives b. p. 165—166°/12 mm. (Found : C, 73·0, 73·6; H, 7·9, 8·2; N, 8·3. Calc. for $C_{10}H_{11}ON$: C, 73·6; H, 8·0; N, 8·6%).

(ii) Epichlorohydrin (21·8 ml.) and methylaniline (26·2 ml.), after reaction as described above except that adequate external cooling was applied at the onset, were heated at 180° for 1½ hours, to give : (*a*) dimethylaniline, b. p. 82°/12 mm. (1 ml.), which exhibited slight fluorescence; (*b*) 3-*N*-methylanilinopropylene oxide (I), b. p. 140—146°/12 mm. (18 ml.), identified as picrate; (*c*) 3-hydroxykairoline, b. p. 156—161°/12 mm. (5 ml.), identified as picrolonate; and (*d*) 1 : 3-di-(*N*-methylanilino)propan-2-ol, b. p. 195—198°/0·25 mm., m. p. 80°, identified by a mixed m. p. No kairoline was isolated in this case, although formation of a very small amount is not precluded. Much residue was again obtained.

Kairoline was identified as methiodide, m. p. 171·5°, and picrate, m. p. 137·5°, both m. p.s being undepressed on admixture with the respective derivatives of commercial (Schuchardt) material. The m. p. of the picrate of the commercial base could not be raised above 125° by the use of neutral organic solvents, but crystallisation from dilute acetic acid gave material of m. p. 134—135°; the impurity was quinoline, and the presence of this or similar substances may be the reason for the wide variation in the m. p. (125° to 145°) recorded in the literature. 3-Hydroxykairoline with nitrous acid gave an orange colour which changed to green on neutralisation with aqueous ammonia. With methylmagnesium iodide 3-hydroxykairoline gave methane, and with phenyl isocyanate in benzene at 100° (1 hour) gave an uncrystallisable oil. No precipitate was formed on treatment with alcoholic picric acid, but with picrolonic acid a sparingly soluble *picrolonate*, m. p. 185° (decomp.), yellow needles from acetone, was obtained (Found : C, 55·85; H, 4·9. $C_{10}H_{11}ON,C_{10}H_8O_5N_4$ requires C, 56·15; H, 4·9%). Warming the base with excess of methyl iodide gave a *methiodide*, m. p. 157° (slight decomp.) (prisms from acetone–ether) considerably variable according to the rate of heating (Found : C, 43·1; H, 5·35; N, 4·45; I, 41·8. $C_{11}H_{14}ONI$ requires C, 43·3; H, 5·25; N, 4·6; I, 41·65%).

1-*Methyl*-1 : 2-*dihydroquinoline* (IV).—This *base*, b. p. 128°/15 mm., was obtained in theoretical yield when 3-hydroxykairoline (5 g.) was heated with powdered potassium hydroxide (5 g.) in a distilling flask at 190°/20 mm., the distillate being redistilled immediately (Found : C, 83·0; H, 7·65; N, 9·6. $C_{10}H_{11}N$ requires C, 82·7; H, 7·6; N, 9·65%). It is a mobile water-insoluble liquid, aqueous-alcoholic solutions of which fluoresce. It formed a methiodide, m. p. 205° (with sublimation), rapidly developed a red colour, and became cloudy and viscous after 24 hours, even in a sealed tube or in the presence of a trace of quinol. It was not re-formed by heating the viscous material, which partly solidified during 7 days. The polymer was insoluble in alcohol, but acetone dissolved the adhering oil, leaving a white powder which dissolved in hot alcohol and was re-precipitated on cooling. Two repetitions of this treatment gave an amorphous *polymer*, m. p. 100° (Found : C, 82·1; H, 8·0%), which darkened during several days, while the m. p. fell to 94—97°.

Conversion of (IV) *into Kairoline.*—To monomeric (IV) (3 g.) in dilute sulphuric acid (15 ml.) at 100° zinc dust (10 g.) was added in portions during 1½ hours, with occasional shaking. The mixture was filtered, made alkaline with aqueous sodium hydroxide, and extracted with ether. The dried extract on distillation gave a stable mobile liquid, identified as kairoline, b. p. 110°/15 mm. (0·5 g.), by a mixed m. p. determination of its picrate.

Production of 3-*Hydroxykairoline from* 1-*Chloro*-3-*N*-*methylanilinopropan*-2-*ol* (II).—The chlorohydrin (II) (5 g.) was heated at 190—200° for 2 hours, gaseous products being evolved. The dark, viscous residue was shaken with a mixture of ether and 5% aqueous sodium hydroxide. The dried ethereal extract yielded dimethylaniline, b. p. 110°/20 mm. (0·5 ml.) (identified as picrate), and 3-hydroxykairoline, b. p. 130—135°/1 mm. (2·5 g.), identified as picrolonate. The remainder was high-boiling material.

Preparation and Reactions of 3-*N*-*Methylanilinopropylene Oxide.*—The crude undistilled chlorohydrin (II) was converted by cold 50% sodium hydroxide solution into 3-*N*-methylanilinopropylene oxide (I), b. p. 120—122°/3 mm., 107°/0·5 mm., n_D^{25} 1·562 (Found : C, 73·6; H, 7·8; N, 8·8. Calc. for $C_{10}H_{11}ON$: C, 73·6; H, 7·95; N, 8·6%), in 74% yield. Eisleb (*loc. cit.*) records b. p. 132—134°/8 mm., 160—162°/30 mm. A 10% yield of 1 : 3-di-(*N*-methylanilino)propan-2-ol was also formed.

The oxide was characterised as *picrate*, m. p. 109°, yellow prisms from alcohol (Found: N, 14·0. $C_{10}H_{13}ON,C_6H_3O_7N_3$ requires N, 14·3%), did not produce methane with methylmagnesium iodide, and gave no precipitate with aqueous *p*-nitrophenylhydrazine hydrochloride. Infra-red analysis (for which we thank Dr. J. B. Willis) showed the absence of hydroxy-groups. The product formed on heating (I) (1·63 g.) and methylaniline (1·25 g.) at 160° for 2 hours solidified on cooling; washing the product with light petroleum gave 1 : 3-di-(*N*-methylanilino)propan-2-ol (IV), m. p. 80°, without recrystallisation.

3-*N*-*Methylanilinopropylene Glycol*.—The *glycol*, b. p. 156—158°/0·5 mm., m. p. 74—75°, plates from benzene–light petroleum, was prepared by heating (I) (5 g.) in 5*N*-sulphuric acid (10 ml.) under gentle reflux for ½ hour, cooling, and carefully neutralising the mixture with concentrated aqueous ammonia (Found: C, 66·55; H, 8·35. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3%). In a first experiment, crystallisation of this glycol, which was difficult to extract from aqueous medium with ether, was effected only after evaporation to dryness and extraction with alcohol–ether, followed by distillation and digestion of the distillate with cold ether; in a second experiment crystallisation was effected by seeding the crude reaction mixture. The glycol was readily soluble in alcohol or benzene, slightly soluble in ether or water, and sparingly so in light petroleum.

Sodium 3-*N*-*Methylanilino*-2-*hydroxypropane*-1-*sulphonate*.—This *salt* (Found: Na, 8·65. $C_{10}H_{14}O_4SNa$ requires Na, 8·6%), m. p. 266°, lustrous plates from 90% alcohol, was obtained when the oxide (I) (1·63 g.) in alcohol was mixed with sodium sulphite (3 g.) and the mixture buffered to neutrality (phenolphthalein) with acetic acid and aqueous sodium acetate. The mixture was then kept at 30° for 18 hours and concentrated. This isethionate is readily soluble in water (*cf.* Lauer and Hill, *J. Amer. Chem. Soc.*, 1936, **58**, 1873).

Attempts to make pure salts, other than the picrate, from (I) were unsuccessful. An uncrystallisable oil was obtained when (I) was heated with excess of methyl iodide for ½ hour. Dry hydrogen chloride was passed into a solution of (I) (1·63 g.) in dry benzene at 0°, with cooling, until the weight had increased by 0·36 g. The mobile oil which separated dissolved by warming to 60° and was not reprecipitated on cooling. Distillation gave a main fraction b. p. 140°/1·2 mm., n_D^{25} 1·572, which contained non-ionic chlorine and was probably the chlorohydrin (II) or an isomer.

N-*Methylanilinomethyl*-*thiairene*(-*propylene Sulphide*) (V).—This *compound*, a pale yellow liquid, b. p. 107—108°/0·1 mm., 154°/12 mm., n_D^{25} 1·606, possessing a slight offensive odour, was obtained (3 g.) when thiourea (2·5 g.) and (I) (4·1 g.) in methanol (20 ml.) were stirred at 60° for 1½ hours, the mixture being then poured into water (100 ml.), extracted with chloroform, dried, distilled, and fractionated to remove unchanged oxide (Found: N, 7·7. $C_{10}H_{13}NS$ requires N, 7·8%). It forms a sparingly soluble *picrate*, yellow pyramid-like crystals (from alcohol), m. p. 76·5° (Found: S, 7·8. $C_{10}H_{13}NS,C_6H_3O_7N_3$ requires S, 7·85%). When the sulphide (V) was heated under reflux with a large excess of methyl iodide for 15 minutes, a crystalline *methiodide* was rapidly precipitated, recrystallisation from alcohol–benzene giving plates, m. p. 147·5° (Found: S, 9·9; I, 40·25. $C_{11}H_{16}NIS$ requires S, 9·95; I, 39·6%), soluble in water, but rapidly polymerised when heated in alkali (*cf.* Dachlauer and Jackel, D.R.-P. 636,708). Nitrogen was readily evolved on treatment of the methiodide with a solution of sodium azide, iodine, and potassium iodide in water.

3-*N*-*Methylanilinopropylene Trithiocarbonate* (VI).—This was obtained as a viscous, malodorous, non-distillable, yellow oil when the oxide (I) (4·1 g.) and excess of potassium methylxanthate were kept in methyl alcohol for 18 hours. The oil was extracted with benzene, the extract washed well with water and methanol and dried, and the benzene evaporated off. Like most trithiocarbonates, it was only sparingly soluble in alcohol, ether, or acetone, but readily soluble in benzene or chloroform. A benzene solution of the undistilled ester was warmed with an excess of alcoholic picric acid and the reddish oil set aside until crystallisation occurred. Recrystallisation from alcohol, in which it is not very soluble, gave yellow crystals of the *picrate*, m. p. 124—125° (Found: S, 19·9. $C_{11}H_{13}NS_3,C_6H_3O_7N_3$ requires S, 19·85%). On attempted distillation of the ester at 0·6 mm., decomposition occurred at 200°, the distillate consisting mainly of dimethylaniline, as shown by its conversion in high yield by picrolonic acid into *dimethylaniline picrolonate*, small yellow prisms (Found: N, 18·05. $C_9H_{11}N,C_{10}H_8O_5N_4$ requires N, 18·2%), m. p. 200° (from alcohol) not depressed on admixture with the authentic picrolonate.

Reaction of Epichlorohydrin with Diphenylamine.—No reaction occurred when a mixture of these compounds was refluxed without a catalyst. Diphenylamine (16·9 g.), epichlorohydrin (13·9 g.), and sodium iodide (10 g.) were refluxed for 5 hours, cooled, decanted from inorganic material, and distilled, first at 15 mm. whereupon a mixture of gaseous hydrogen chloride and iodide distilled together with unchanged epichlorohydrin below 140°, and then at 1·5 mm. whereupon unchanged diphenylamine, b. p. 150—170°, and crude 3-hydroxy-1-phenyl-1 : 2 : 3 : 4-tetrahydroquinoline, b. p. 175—183°, were collected. The latter was purified by redistillation and solidified on storage. Recrystallisation from benzene–light petroleum gave a halogen-free product (7 g.), m. p. 78—79°; m. p. 79° is recorded in D.R.-P. 284,291. This compound (1 g.) and phenyl *iso*cyanate (1·4 g.) in dry benzene, when kept in a sealed tube for 3 days at 30°, gave a *carbanilate*, m. p. 127° (Found: N, 8·35. $C_{23}H_{22}O_3N_2$ requires N, 8·15%), needles from alcohol.

Reaction of Epichlorohydrin with p-*Toluidine*.—The use of aqueous alcohol as in the method of Cohn and Friedlaender (*loc. cit.*) gave 1-chloro-3-*p*-toluidinopropan-2-ol, leaflets (from alcohol), m. p. 81—82°. No distillate was obtained when this product was heated at 220°/0·8 mm.; there was a small sublimate of a basic hydrochloride. On cooling, the contents of the flask set to a hard resin which was only sparingly soluble in aqueous or organic solvents. When the chlorohydrin was stirred in benzene with 30% sodium hydroxide solution for 1 hour and the benzene was evaporated off at room temperature, a similar glassy resin was obtained, which has possible technical applications.

The micro-analyses were made by N. L. Lottkowitz. One of us (W. E. S.) acknowledges financial assistance from the Commonwealth Reconstruction Training Scheme.

Organic Chemistry Laboratory,
University of Melbourne.

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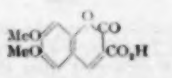
182. *The Chemistry of Fungi. Part IX.* 3 : 4-*Dihydrocoumarins.*

By F. M. Dean, Alexander Robertson, and W. B. Whalley.

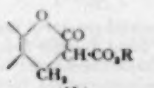
The preparation of typical 3 : 4-dihydrocoumarin-3-carboxylic acids and 3-acetyl-3 : 4-dihydrocoumarins by hydrogenation of the corresponding coumarin derivatives is described. From an examination of the properties of these products it has been concluded that *O*-dimethylcitromycin is not a derivative of 3 : 4-dihydrocoumarin as proposed in Part III (*loc. cit.*).

It is probable that the "diacetyl" derivative of 3 : 4-dihydrocoumarin described by Karstner (*loc. cit.*) is 6-acetoacetyl-3 : 4-dihydrocoumarin.

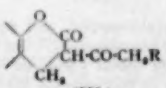
From the evidence then available it was concluded in Part III (*J.*, 1949, 848) that citromycin and its dimethyl ether possessed a linear type of structure which could be envisaged as a cyclisation product of a 3 : 4-dihydrocoumarin derivative type (III; R = Ac). Further, the methylene group in the 4-position of the coumarin residue (III) was considered to be involved in the novel oxidation $\cdot CH_2 \longrightarrow \cdot CH(OH) \longrightarrow \cdot CO$ effected with ozone and in the hydroxylation process with lead tetra-acetate, a view which appeared to receive support from studies on the oxidation of xanthens under similar conditions Part VIII (*J.*, 1949, 1567). The experiments described in the present communication were undertaken during our search for collateral evidence in support of the proposed structure for *O*-dimethylcitromycin and had three objectives: (*a*) to investigate the preparation of dihydrocoumarins of types (II) and (III; R = H) which could be employed as intermediates in the synthesis of (III; R = Ac) and hence of *O*-dimethyl-



(I.)



(II.)



(III.)

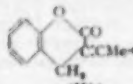
citromycin; (*b*) to compare the 2 : 4-dinitrophenylhydrazone of (III; R = H) with the corresponding derivative, m. p. 282° (decomp.), of a product which was considered to be (III; R = H) (Part III, *loc. cit.*); and (*c*) to examine the behaviour of compounds of types (II) and (III; R = H) towards lead tetra-acetate and hydrolytic agents because compounds having structures (II) and (III; R = H) would provide a closer analogy with *O*-dimethylcitromycin than do the xanthens (Part VIII, *loc. cit.*).

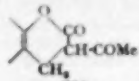
The preparation of 3 : 4-dihydrocoumarin-3-carboxylic acids containing a quinol nucleus by the hydrogenation of the corresponding coumarin-3-carboxylic acids has been extensively studied by Smith and his collaborators (see, *e.g.*, *J. Amer. Chem. Soc.*, 1936, **58**, 304) who have also described the preparation of 6-hydroxy- and 6-methoxy-3-acetyl-5 : 7 : 8-trimethyl-3 : 4-dihydrocoumarin by the hydrogenation of 6-hydroxy-3-acetyl-5 : 7 : 8-trimethylcoumarin and its methyl ether (*ibid.*, 1937, **59**, 667). In the present work similar methods have been employed.

The hydrogenation of coumarin-3-carboxylic acid in the form of its sodium salt with a palladium–charcoal catalyst gave a mixture of the expected 3 : 4-*dihydrocoumarin-3-carboxylic acid* with its hydrated derivative, *2-hydroxybenzylmalonic acid*, which became the main product when 3 : 4-dihydrocoumarin-3-carboxylic acid, which separated initially on acidification of the filtered reaction mixture, was kept in contact with the mother-liquor. Methyl 2-hydroxybenzylmalonate was prepared by means of diazomethane and on distillation gave an almost quantitative yield of *methyl* 3 : 4-*dihydrocoumarin-3-carboxylate* which was also formed by the hydrogenation of coumarin-3-carboxylic acid in methanol. The hydrogenation of 6 : 7-*dimethoxycoumarin-3-carboxylic acid* (I) as its sodium salt furnished a mixture of 6 : 7-dimethoxy-3 : 4-dihydrocoumarin-3-carboxylic acid (II; R = H) and the corresponding benzylmalonic acid which on distillation in a vacuum gave rise to 6 : 7-dimethoxy-3 : 4-dihydrocoumarin. Treatment of the mixed acids with an excess of ethereal diazomethane gave the esters from which *methyl* 6 : 7-*dimethoxy-3 : 4-dihydrocoumarin-3-carboxylate* (II; R = Me) was isolated. When it was found that the acid chloride of 3 : 4-dihydrocoumarin-3-carboxylic acid could not be obtained by one or other of the standard methods, the preparation of other members of this series was abandoned.

Application of the hydrogenation process to 3-acetylcoumarin gave an excellent yield of 3-*acetyl-3 : 4-dihydrocoumarin* apparently as a keto–enol equilibrium mixture, in all probability (IV; R = H) and (V), from which the pure keto-form giving a negative ferric reaction was isolated. Acetylation of the mixture gave the *acetate* (IV; R = Ac) of the enolic compound which, as expected, did not react with ketonic reagents. The independent synthesis of 3-acetyl-

3 : 4-dihydrocoumarin in small yield by the interaction of 2-*(ethyl carbonato)benzylacetone* and ethyl carbonate in the presence of sodium served to confirm the structure of the compound. In contrast to the behaviour of the parent 3-acetylcoumarin the hydrogenation of 6 : 7-dimethoxy-3-acetylcoumarin was much slower and the main product was 6 : 7-*dimethoxy*-3-*ethylcoumarin* accompanied by only small amounts of the required 6 : 7-*dimethoxy*-3-*acetyl*-3 : 4-*dihydrocoumarin* (III; R = H), the 2 : 4-dinitrophenylhydrazone, m. p. 228°, of which was not identical with the product, m. p. 282° (decomp.), obtained from *O*-dimethylcitromycin (Part III, *loc. cit.*); the yield of (III; R = H) was slightly increased when platinum–charcoal was employed as the catalyst in place of palladium–charcoal. Consequently we examined the hydrogenation of a number of analogous 3-acetylcoumarins under similar conditions.


(IV.)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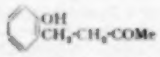
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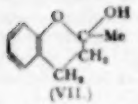
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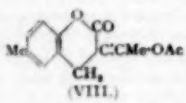
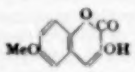

(VIII.)


(IX.)

3-*Acetyl*-6-*methyl*- and 6-*methoxy*-3-*acetyl*-*coumarin* behaved normally, giving the respective 3 : 4-*dihydrocoumarins*. On the other hand 3-*acetyl*-7-*methyl*- and 7-*methoxy*-3-*acetyl*-*coumarin* gave only small yields of the 3 : 4-*dihydrocoumarins* which were separated from the main products of the reaction by taking advantage of the fact that 3-acetyl-3 : 4-dihydrocoumarins readily form chelated derivatives on treatment with aqueous copper acetate. From 3-acetyl-7-methylcoumarin the principal hydrogenation product was a compound which was readily differentiated from 7-*methyl*-3-*ethylcoumarin* and appeared to be 7-*methyl*-3-1′-*hydroxyethylcoumarin*. With 7-methoxy-3-acetylcoumarin the main product was 7-*methoxy*-3-*ethylcoumarin*, whilst 7-hydroxy-3-acetylcoumarin gave only the corresponding 3-ethylcoumarin.

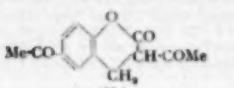
In their behaviour towards oxidising and hydrolytic agents the 3 : 4-dihydrocoumarin derivatives which have been examined showed a marked contrast to *O*-dimethylcitromycin under comparable conditions. 3 : 4-Dihydrocoumarin-3-carboxylic acid and its methyl ester, and 3-acetyl-3 : 4-dihydrocoumarin together with its 6-methyl and 6-methoxy-derivatives, readily underwent dehydrogenation with lead tetra-acetate, regenerating the parent coumarin derivatives which did not appear to be accompanied by detectable amounts of products oxygenated at the 4-position. In this connection it is of interest to note that 6-methoxy- and 6 : 7-dimethoxy-3-acetyl-3 : 4-dihydrocoumarin are readily dehydrogenated to the corresponding coumarins when solutions of the compounds are exposed to atmospheric oxygen, whilst in an alcoholic solution of 2 : 4-dinitrophenylhydrazine the 2 : 4-*dinitrophenylhydrazone* of 3-acetyl-3 : 4-dihydrocoumarin is oxidised to the 2 : 4-*dinitrophenylhydrazone* of 3-acetylcoumarin. The action of lead tetra-acetate clearly proceeds by the replacement of the active hydrogen atom in the 3-position of the 3-carboxy- or 3-acetyl-dihydrocoumarin by an acetoxy-group followed by the loss of acetic acid and the formation of the coumarin system. This reaction mechanism is in keeping with the failure of the reagent to dehydrogenate 3 : 4-dihydrocoumarin, its 6 : 7-dimethoxy-derivative, or the *acetate* (VIII) of the enolic form of 6-methyl-3-acetyl-3 : 4-dihydrocoumarin. On ozonolysis 6-methoxy-3-acetyl-3 : 4-dihydrocoumarin furnished a mixture from which 3-*hydroxy*-6-*methoxycoumarin* and 2-hydroxy-4-methoxybenzaldehyde were isolated, but a search failed to reveal the presence of 4-hydroxy-6-methoxy-3-acetylcoumarin.

In their behaviour on hydrolysis with acidic and alkaline reagents 3-acetyl-3 : 4-dihydrocoumarins differ markedly from *O*-dimethylcitromycin. With these reagents the lactone ring of the dihydrocoumarin is opened and carbon dioxide is then eliminated, resulting in the formation of 2-hydroxybenzylacetones which, in the examples studied, have been isolated in the ketonic and cyclic forms represented by types (VI) and (VII) respectively. The alkali-insoluble cyclic forms readily give the 2 : 4-dinitrophenylhydrazones derived from the ketones.

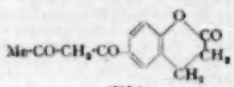
From our examination of the properties of 3 : 4-dihydrocoumarins it now seems reasonably certain that the citromycin molecule does not contain a 3 : 4-dihydrocoumarin residue as suggested in Part III (*loc. cit.*). Hydrolysis of citromycin or its dimethyl ether under a variety of conditions (Part III and unpublished work) has failed to yield products containing a

2-hydroxybenzylacetone nucleus. Further, the proposed formula for citromycin and its ether (Part III) implied that in the degradation of the ether to 2-hydroxy-4 : 5-dimethoxyacetophenone and -benzoic acid with alkali the methylene group in the 4-position of the 3 : 4-dihydrocoumarin residue was oxidised, whereas the authentic 3 : 4-dihydrocoumarin derivatives examined do not undergo degradation in this way.

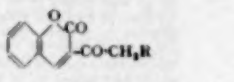
In the course of exploratory experiments on the synthesis of 3-acetyl-3 : 4-dihydrocoumarins by alternate routes we examined the reaction reported by Kaestner ("Newer Methods of Preparative Organic Chemistry," 1948, New York, p. 296) by which 3 : 4-dihydrocoumarin is stated to be acetylated with the aid of boron trifluoride, giving the 3 : 6-diacetyl derivative (X). On the basis of this result it seemed reasonable to expect that 3 : 4-dihydrocoumarins substituted in the 6-position would give the 3-acetyl derivative (type III, R = H). This reaction failed, however, in the case of 6 : 7-dimethoxy-3 : 4-dihydrocoumarin, a result which led us to examine the diacetyl derivative of 3 : 4-dihydrocoumarin described by Kaestner who did not, however, record the melting point of the compound. Though our investigation is not yet complete, it appears that the compound is not 3 : 6-diacetyl-3 : 4-dihydrocoumarin (X), but, from the following considerations is, in all probability, 6-acetoacetyl-3 : 4-dihydrocoumarin (XI) :



(X.)



(XI.)



(XII.)

(*a*) Kaestner's compound gives a deep-red ferric reaction typical of compounds containing the group ·CO·CH$_2$·CO·, whereas 3-acetyl-3 : 4-dihydrocoumarins invariably give a characteristic intense purple ferric reaction which we would not expect to be modified by the presence of an acetyl group in the 6-position.

(*b*) The compound is hydrolysed with 2N-aqueous sodium hydroxide to a product believed to be 6-acetyl-3 : 4-dihydrocoumarin (cf. Kaestner *loc. cit.*), whereas dihydrocoumarins *C*-acetylated in the 3-position invariably give a 2-hydroxybenzylacetone derivative.

(*c*) With lead tetra-acetate the compound reacts rapidly yielding an oil which retains the red ferric reaction—a property in keeping with the acetoxylation of a β-diketone, *i.e.*, ·CO·CH$_2$·CO ⟶ ·CO·CH(O·COMe)·CO·, whereas a dihydrocoumarin of the type (X) would be expected to undergo dehydrogenation yielding 3 : 6-diacetylcoumarin which would not give a ferric reaction.

(*d*) As far as we are aware β-ketonic esters cannot be prepared by the boron trifluoride–acetic anhydride method, and dihydrocoumarins substituted in the 6-position do not appear to form the corresponding 3-acetyl-3 : 4-dihydrocoumarins by this method. The latter compounds form comparatively stable complexes with boron trifluoride which do not react further and hence we were unable to prepare, by this route, 3-acetoacetyl-3 : 4-dihydrocoumarins cyclisation of which might be expected to give compounds having the type of structure proposed for *O*-dimethylcitromycin in Part III (*loc. cit.*). It would appear, therefore, that in Kaestner's preparation acetylation of dihydrocoumarin occurs first in the 6-position and, as the methyl of the *C*-acetyl group is more reactive than the α-methylene of an ester or lactone, further acetylation then takes place giving the 6-acetoacetyl derivative (XI) by way of the boron trifluoride complex. It is of interest to note that the acetylation of 3-acetylcoumarin (XII; R = H) by the same method gave 3-acetoacetylcoumarin (XII; R = Ac) which Trenknerowna (*Roczniki Chem.*, 1936, **16**, 6, 10) has synthesised by an independent route and which has a ferric reaction similar to Kaestner's compound.

Experimental.

3 : 4-*Dihydrocoumarin-3-carboxylic Acid.*—The sodium salt of coumarin-3-carboxylic acid in water (150 ml.) was prepared as a slurry from the acid (4 g.) and sodium hydrogen carbonate (2·1 g.) and subjected to hydrogenation with a palladium–charcoal catalyst (from 1 g. of charcoal and 0·4 g. of palladium chloride) and hydrogen at 62 lbs./sq. in. for 4 hours. On acidification with hydrochloric acid the filtered solution deposited during 10 minutes 3 : 4-*dihydrocoumarin-3-carboxylic acid* as a mass of fine needles (Found : C, 62·5; H, 4·5. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%) which had m. p. 142° after recrystallisation from water or ethyl acetate; the yield was somewhat variable, but in general about 2·5 g. were obtained from 4 g. of coumarin-3-carboxylic acid. This dihydro-acid is sparingly soluble in warm ligroin and readily soluble in alcohol or aqueous sodium hydrogen carbonate, and on being kept at 150—160° for 15 minutes decomposed with the evolution of carbon dioxide, giving a quantitative yield of 3 : 4-dihydrocoumarin, b. p. 178°/0·1 mm., which was identified by being converted into the

hydrazide, m. p. 166°, of melilotic acid (undepressed on admixture with an authentic specimen) (Pschorr and Einbeck, *Ber.*, 1905, **38**, 2070, gave m. p. 164—165°). Prepared by means of diazomethane, *methyl* **3 : 4-***dihydrocoumarin-3-carboxylate* formed colourless prisms, m. p. 98—100°, from 85% alcohol, insoluble in aqueous sodium hydrogen carbonate and slowly soluble in 2*N*-aqueous sodium hydroxide (Found : C, 64·2; H, 5·0. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%).

When the crude **3 : 4**-dihydrocoumarin-3-carboxylic acid was left in contact with the acidified mother-liquor the solid dissolved, and on being kept for several weeks the solution gradually deposited *2-hydroxybenzylmalonic acid* in large colourless prisms, m. p. 142° (decomp.), readily soluble in aqueous sodium hydrogen carbonate [Found : C, 57·0; H, 4·9%; equiv. (by titration), 109·4. $C_{10}H_{10}O_5$ requires C, 57·2; H, 4·8%; equiv., 105]. A small quantity of this malonic acid was occasionally obtained from the solution left after the separation of **3 : 4**-dihydrocoumarin-3-carboxylic acid. Although a mixture of this dibasic acid and **3 : 4**-dihydrocoumarin-3-carboxylic acid did not show a depression in the melting point, it was clear that the two substances were not identical. Esterification of the dibasic acid with ethereal diazomethane yielded a liquid which, on distillation in a vacuum at 134—136°/0·5 mm., was completely converted into methyl **3 : 4**-dihydrocoumarin-3-carboxylate, m. p. and mixed m. p. 98°, after purification.

Hydrogenation of coumarin-3-carboxylic acid (10 g.) in methanol (200 ml.) with a palladium–charcoal catalyst and hydrogen at 100 lbs./sq. in. gave an oil which, on distillation in a vacuum, partly crystallised. The solid, which slowly separated, was freed from adhering liquid by means of a porous tile and recrystallised from ethyl acetate–ligroin, giving methyl **3 : 4**-dihydrocoumarin-3-carboxylate, m. p. and mixed m. p. 97—98° (Found : C, 63·9; H, 4·8%). This compound reacted with warm 50% hydrazine hydrate solution, giving the *2-hydroxybenzylmalonodihydrazide* which formed large colourless prisms, m. p. 236—240° (decomp.), from warm water (Found : C, 50·1; H, 5·8; N, 23·5. $C_{10}H_{14}O_3N_4$ requires C, 50·4; H, 5·9; N, 23·8%). The oil left after the separation of the crude methyl **3 : 4**-dihydrocoumarin-3-carboxylate appeared to consist mainly of **3 : 4**-dihydrocoumarin since it gave the hydrazide, m. p. and mixed m. p. 166°, of melilotic acid.

Dehydrogenation of **3 : 4***-Dihydrocoumarin-3-carboxylic Acid.*—When powdered lead tetra-acetate (1 g.) was added to a solution of the acid (0·5 g.) in acetic acid (10 ml.) a white lead salt separated during 3 hours, and the mixture then had a negative starch–iodide reaction. Treatment of the solid with warm dilute nitric acid gave a yellow solution which on being cooled deposited coumarin-3-carboxylic acid in colourless prisms (0·18 g.), m. p. 202°, identical with an authentic specimen. When the acid was replaced by methyl **3 : 4**-dihydrocoumarin-3-carboxylate (0·5 g.) in the foregoing experiment and the mixture kept for 24 hours and then diluted with water, methyl coumarin-3-carboxylate separated in colourless needles, m. p. 119—120°, after purification, identified by comparison with an authentic specimen.

6 : 7*-Dimethoxycoumarin-3-carboxylic Acid* (I).—2-Hydroxy-**4 : 5**-dimethoxybenzaldehyde (3 g.) and sodium cyanoacetate (50 ml. of a solution prepared according to Phelps and Tillotson, *Amer. Journ. Science*, 1908, **26**, 275) were caused to react by means of sodium hydroxide (10 g.) in water (10 ml.) during 24 hours. Acidification of the reaction mixture with hydrochloric acid furnished a deep-yellow product which was heated under reflux with concentrated hydrochloric acid (20 ml.) and water (30 ml.) for 10 minutes, giving rise to the *coumarin-3-carboxylic acid*. Recrystallised from alcohol, this compound formed lemon-yellow needles (3 g.), m. p. 266° (decomp.), insoluble in water or ligroin and readily soluble in ethyl acetate, chloroform, or aqueous sodium hydrogen carbonate (Found : C, 57·5; H, 3·9. $C_{11}H_{10}O_6$ requires C, 57·6; H, 4·0%). Prepared by means of ethereal diazomethane, the *methyl* ester separated from alcohol in yellow prisms, m. p. 212°, soluble in benzene or ethyl acetate (Found : C, 59·3; H, 4·6. $C_{12}H_{12}O_6$ requires C, 59·1; H, 4·6%). Alcoholic solutions of the acid or its ester exhibited an intense blue fluorescence.

Methyl **6 : 7***-Dimethoxy-***3 : 4***-dihydrocoumarin-3-carboxylate* (II; R = Me).—Hydrogenation of the foregoing coumarin-3-carboxylic acid (0·5 g.), dissolved in water (25 ml.) containing sodium hydrogen carbonate (0·17 g.), with 20% palladium–charcoal (1 g.) and hydrogen at 60 lbs./sq. in. for 4 hours gave a mixture consisting mainly of 2-hydroxy-**4 : 5**-dimethoxybenzylmalonic acid with small amounts of **6 : 7**-dimethoxy-**3 : 4**-dihydrocoumarin-3-carboxylic acid which could not be conveniently separated. Recrystallised from water this product formed colourless needles (0·3—0·45 g.), m. p. 120° (decomp.), readily soluble in aqueous sodium hydrogen carbonate [Found : C, 50·5; H, 5·5%; equiv. (by titration) 135. Calc. for $C_{12}H_{14}O_6$: C, 57·1; H, 4·8%; equiv., 252. Calc. for $C_{12}H_{14}O_6,H_2O$: C, 50·0; H, 5·6%; equiv., 138]. On distillation at 155—160°/0·14 mm., the recrystallised product (1 g.) gave **6 : 7**-dimethoxy-**3 : 4**-dihydrocoumarin (0·7 g.), m. p. 79—80° (Part II, *J.*, 1949, 565), and on treatment with an excess of ethereal diazomethane furnished an oil (1 g.) which, on being kept, deposited *methyl* **6 : 7***-dimethoxy-***3 : 4***-dihydrocoumarin-3-carboxylate* (II; R = Me) (0·1 g.), insoluble in cold dilute aqueous sodium hydroxide. Since it was readily soluble in alkali and on distillation at 190/0·1 mm. gave (II; R = Me) (0·7 g.), the residual oil appeared to be mainly methyl 2-hydroxy-**4 : 5**-dimethoxybenzylmalonate. Recrystallised from ethanol, the ester (II; R = Me) formed rectangular prisms, m. p. 151—152° (Found : C, 58·4; H, 5·3. $C_{13}H_{16}O_6$ requires C, 58·6; H, 5·3%). Lead tetra-acetate (0·16 g.) in acetic acid (8 ml.) was added during 1 hour to a solution of methyl **6 : 7**-dimethoxy-**3 : 4**-dihydrocoumarin-3-carboxylate (0·1 g.) in acetic acid (8 ml.), and 3 hours later the mixture was diluted with water (50 ml.), giving methyl **6 : 7**-dimethoxycoumarin-3-carboxylate which slowly separated in long lemon-yellow needles, m. p. 212°, identical with an authentic specimen.

3*-Acetyl-***3 : 4***-dihydrocoumarin.*—(*a*) 3-Acetylcoumarin (Knoevenagel, *Ber.*, 1898, **31**, 732) formed a **2 : 4***-dinitrophenylhydrazone* which separated from acetic acid in orange prisms, m. p. 257—258° (decomp.) (Found : C, 55·2; H, 3·5; N, 14·9. $C_{17}H_{14}O_6N_4$ requires C, 55·4; H, 3·3; N, 15·3%).

A suspension of 3-acetylcoumarin (5 g.) in methanol (200 ml.) was agitated with palladium–charcoal (from 1 g. of charcoal and 0·1 g. of palladium chloride) and hydrogen at 60 lbs./sq. in. at room temperature for 1 hour and the filtered reaction mixture evaporated in a vacuum at 40°, leaving a colourless residue (4·8 g.), m. p. ~58°; traces of mineral acid in the catalyst or evaporation at higher temperatures caused decomposition of the product. Recrystallisation of the residual solid from aqueous methanol or

benzene–ligroin gave **3-*acetyl*-3 : 4-*dihydrocoumarin*** in colourless elongated plates, m. p. 62°, giving a deep-purple ferric reaction in alcohol (Found : C, 69·8; H, 5·2. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). This compound is insoluble in aqueous sodium hydrogen carbonate, sparingly soluble in cold ligroin, and readily soluble in benzene, alcohol, chloroform, or 1% aqueous sodium hydroxide. The *oxime* separated from aqueous alcohol in colourless prisms, m. p. 174° (decomp.) after becoming reddish-brown at 160—170°, which are readily soluble in dilute aqueous sodium hydroxide (Found : C, 65·0; H, 5·4; N, 6·6. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·8%). Crystallised from alcohol, the *semicarbazone* was obtained in colourless prisms, m. p. 188°, which exhibited a royal-blue ferric reaction in alcohol and were instantly soluble in cold 2*N*-aqueous sodium hydroxide (Found : C, 58·2; H, 5·5; N, 17·3. $C_{12}H_{14}O_3N_3$ requires C, 58·3; H, 5·3; N, 17·0%). The **2 : 4-*dinitrophenylhydrazone*** separated from ethyl acetate in yellow needles, m. p. 174° (Found : C, 55·3; H, 3·7; N, 14·9. $C_{17}H_{14}O_6N_4$ requires C, 55·1; H, 3·8; N, 15·1%). When the crude hydrazone was allowed to remain in contact with the excess of 2 : 4-dinitrophenylhydrazine solution for about a week, its colour changed to deep orange. Recrystallised from ethyl acetate the product then gave the 2 : 4-dinitrophenylhydrazone of 3-acetylcoumarin in orange prisms, m. p. 258° (decomp.), identified by comparison with an authentic specimen. Addition of aqueous copper acetate to an alcoholic solution of 3-acetyl-3 : 4-dihydrocoumarin gave a precipitate of the insoluble copper derivative from which the dihydrocoumarin was regenerated by treatment with cold dilute mineral acid and ether, followed by evaporation of the dried ethereal liquor.

A mixture of 3-acetyl-3 : 4-dihydrocoumarin (0·5 g.), acetic anhydride (2 ml.), and pyridine (2 ml.) was warmed on the steam-bath for 10 minutes, kept for 24 hours, and poured into an excess of dilute hydrochloric acid. The resulting oily O-*acetyl* derivative solidified in contact with a little alcohol and then crystallised from aqueous alcohol in slender prisms (0·4 g.), m. p. 65—66°, insoluble in cold dilute aqueous sodium hydroxide and having a negative ferric reaction (Found : C, 67·5; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). Mixed with the parent compound the acetyl derivative had m. p. 38—50°.

During numerous hydrogenation experiments with 3-acetyl-3 : 4-dihydrocoumarin it was found that the m. p. of the product varies between 58° and 63° but the product which separated from alcoholic solvents usually had m. p. 62° and, when fused, allowed to solidify, and then re-heated, this material melted again at 62°. After being kept for several months a sample, which originally had m. p. 62°, melted at 66°. On one occasion the spontaneous evaporation of a dilute benzene–light petroleum (b. p. 60—80°) solution of a sample, m. p. 62°, which had been crystallised several times from dilute methanol, gave large prisms, m. p. 67°, which appeared to be the pure keto-form (V), since it had a negative ferric reaction in alcohol and instantaneously gave the 2 : 4-dinitrophenylhydrazone, m. p. 172°, identical with that obtained from the material, m. p. 62°. When a solution of this apparently pure keto-compound in alcohol was warmed, cooled, and treated with a drop of aqueous ferric chloride it gave the intense purple colour, indicating the presence of the enolic form in the solution. Repeated fusion, followed by cooling, of the pure keto-compound gave the product, m. p. 62°. A mixture of the latter and the keto-compound, m. p. 67°, had m. p. 63—66° which changed to 62° on repeated fusion.

(*b*) Ethyl chloroformate (2·0 g.) was added drop-wise to a vigorously agitated solution of 2-hydroxybenzylacetone (Harries, *Ber.*, 1891, **24**, 3180) (2 g.) in a slight excess of N-aqueous sodium hydroxide, and one hour later the resulting 2-(*ethyl carbonato*)*benzylacetone* was isolated with ether and purified by distillation, being obtained as a colourless oil (1·7 g.), b. p. 125—128°/0·2 mm., readily soluble in the usual organic solvents except ligroin (Found : C, 66·9; H, 6·9. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·9%). A mixture of this ketone (1·7 g.), pulverised sodium (1 g.), and ethyl carbonate (10 g.) was kept at 80° for 3 hours and the resulting flocculent precipitate was collected, washed with ether, dried, and dissolved in water covered with a layer of ether. This mixture was saturated with carbon dioxide, the ethereal layer was separated and evaporated, a solution of the oily residue in a little alcohol was treated with saturated aqueous copper acetate, and the resulting green precipitate (80 mg.) was washed with water, alcohol, and ether and decomposed with 5% sulphuric acid in the presence of ether, giving 3-acetyl-3 : 4-dihydrocoumarin (50 mg.) which formed colourless prisms, m. p. 62—63°, from light petroleum (b. p. 60—80°), identical with a specimen prepared by method (*a*), and gave the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 170°. Left in contact with 2 : 4-dinitrophenylhydrazine solution the latter derivative gave rise to the 2 : 4-dinitrophenylhydrazone of 3-acetylcoumarin, m. p. 257—258° (decomp.).

When the pale yellow solution of 3-acetyl-3 : 4-dihydrocoumarin (0·5 g.) in N-aqueous sodium hydroxide (6 ml.) was heated on the steam-bath for ½ hour a pale yellow oil (negative ferric reaction) separated and was isolated from the cooled mixture with ether. Acidification of the residual alkaline liquor, followed by extraction with ether, gave a small amount of a phenolic product. These compounds, which are respectively 2-hydroxy-2-methylchroman and its isomeride 2-hydroxybenzylacetone (Harries, *Ber.*, 1891, **24**, 3180), have a characteristic pleasant odour and give the same **2 : 4-*dinitrophenylhydrazone***, which forms bright yellow prisms, m. p. 152°, identified by comparison with an authentic specimen (Found : C, 55·3; H, 4·5; N, 16·3. $C_{15}H_{14}O_6N_4$ requires C, 55·8; H, 4·7; N, 16·3%).

When lead tetra-acetate (1·1 g.) was added to a solution of 3-acetyl-3 : 4-dihydrocoumarin (0·5 g.) in acetic acid (15 ml.) the mixture became slightly warm and the lead salt gradually dissolved. 2 Hours later the resulting pale yellow solution gave a negative test for quadrivalent lead and, on the addition of an excess of water, deposited 3-acetylcoumarin as an oil which quickly solidified and then crystallised from dilute methanol in pale yellow prisms, m. p. 123°, undepressed on admixture with an authentic specimen. The 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 258° (decomp.).

3-*Acetyl*-6-*methyl*-3 : 4-*dihydrocoumarin*.—Prepared by the hydrogenation of 3-acetyl-6-methylcoumarin (Chuit and Bolsing, *Bull. Soc. chim.*, 1915, **35**, 89) (2 g.), **3-*acetyl*-6-*methyl*-3 : 4-*dihydrocoumarin*** (1·9 g.) separated from ligroin and then dilute alcohol in colourless prisms, m. p. 71—73°, soluble in hot water, alcohol, or ethyl acetate, and giving an intense purple ferric reaction in alcohol (Found : C, 71·1; H, 5·7. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). The **2 : 4-*dinitrophenylhydrazone*** formed orange-yellow prisms, m. p. 195—196°, from ethyl acetate (Found : C, 56·0; H, 4·1; N, 14·3. $C_{18}H_{16}O_6N_4$ requires C, 56·3; H, 4·2; N, 14·6%). The ***semicarbazone*** separated from alcohol and then methanol in colourless prisms or needles, m. p. 265° (decomp.), readily soluble in 2*N*-aqueous sodium hydroxide and giving a

royal-blue ferric reaction in alcohol (Found: C, 59·9; H, 6·0; N, 16·4. $C_{12}H_{13}O_4N_3$ requires C, 59·7; H, 5·8; N, 16·1%).

Acetylation of 3-acetyl-6-methyl-3 : 4-dihydrocoumarin (2 g.) with acetic anhydride (6 ml.) and pyridine (3 ml.) at room temperature for 16 hours gave an oily solid which, after having been drained on a porous tile, was crystallised from dilute alcohol and then dilute methanol, giving the *acetate* (VIII) of the enolic form of the coumarin in colourless shining plates, m. p. 125° (Found: C, 68·1; H, 5·8. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). This compound, which is soluble in benzene and in hot ligroin, gives a negative ferric reaction in alcohol and does not react with 2 : 4-dinitrophenylhydrazine.

A solution of 3-acetyl-6-methyl-3 : 4-dihydrocoumarin (1 g.) in 2*N*-sodium hydroxide (10 ml.) was heated on the steam-bath for ½ hour, cooled, and extracted with ether. Evaporation of the dried ethereal extract left a neutral oil, whilst saturation of the residual alkaline liquor with carbon dioxide followed by extraction with ether gave a phenolic oil. These phenolic and neutral products, which had similar odours and became purple on being heated, appear to be 2-hydroxy-4-methylbenzylacetone and its cyclic form, 2-hydroxy-2 : 6-dimethylchroman, respectively, since they give rise to the same 2 : 4-*dinitrophenylhydrazone*, forming orange plates, m. p. 165—166°, from dilute alcohol, readily soluble in 1% aqueous sodium hydroxide (Found: C, 57·4; H, 5·4. $C_{17}H_{16}O_5N_4$ requires C, 57·0; H, 5·0%).

Oxidation of 3-acetyl-6-methyl-3 : 4-dihydrocoumarin (1 g.) with lead tetra-acetate (2·1 g.) in acetic acid (15 ml.) at room temperature for 2 hours gave 3-acetyl-6-methylcoumarin (0·85 g.) which formed pale yellow plates, m. p. 131°, from methanol, identical with an authentic specimen. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange prisms, m. p. 256—258°, undepressed on admixture with an authentic specimen (Found: N, 14·9. $C_{18}H_{14}O_6N_4$ requires N, 14·7%).

6-*Methoxy*-3-*acetylcoumarin*.—A few drops of piperidine were added to a mixture of 2-hydroxy-4-methoxybenzaldehyde (Tiemann and Muller, *Ber.*, 1881, **14**, 1990) (10 g.) and ethyl acetoacetate (10 ml.), and the reaction was completed by heating the deep-yellow solution on the steam-bath for 10 minutes. On being cooled the reaction mixture deposited 6-*methoxy*-3-*acetylcoumarin* as a yellow crystalline mass which, after the addition of alcohol (10 ml.), was collected and purified from this solvent, forming brilliant yellow plates (12 g.), m. p. 182—183° (Found: C, 65·9; H, 4·8. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·6%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in diamond-shaped plates, m. p. 242—243° (Found: N, 14·3. $C_{18}H_{14}O_7N_4$ requires N, 14·1%).

6-*Methoxy*-3-*acetyl*-3 : 4-*dihydrocoumarin*.—Hydrogenation of the foregoing coumarin (1 g.) in methanol (200 ml.) with palladium–charcoal and hydrogen at 60 lbs./sq. in., followed by evaporation of the filtered reaction mixture in a vacuum at 40°, gave a gummy solid (0·95 g.) which was purified by repeated crystallisation from alcohol and then light petroleum (b. p. 60—80°), furnishing 6-*methoxy*-3-*acetyl*-3 : 4-*dihydrocoumarin* in pale yellow prisms, m. p. 82—84°. It was observed during the purification from alcohol that each time the compound was dissolved in the solvent a small amount of a highly insoluble yellow product was formed which was found to be 6-methoxy-3-acetylcoumarin arising by the atmospheric oxidation of the 3 : 4-dihydrocoumarin in alcoholic solution. Purified from alcohol, the 6-methoxy-3-acetylcoumarin formed yellow needles, m. p. and mixed m. p. 182—183°, and gave the 2 : 4-dinitrophenylhydrazone, m. p. 242°. When the isolation and purification of the hydrogenation product were carried out in an atmosphere of nitrogen, 6-methoxy-3-acetyl-3 : 4-dihydrocoumarin was obtained in colourless prisms, m. p. 82—84°, giving a purple ferric reaction in alcohol (Found: C, 65·6; H, 5·3. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). On exposure to air alcoholic solutions of this compound absorb oxygen and give a quantitative yield of 6-methoxy-3-acetylcoumarin. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in light-orange spearheads, m. p. 184—185° (Found: C, 54·0; H, 4·0; N, 14·0. $C_{18}H_{14}O_7N_4$ requires C, 54·0; H, 4·0; N, 14·0%). The *semicarbazone* formed large flat prisms, m. p. 188—189°, from alcohol, readily soluble in 2*N*-aqueous sodium hydroxide and giving a royal-blue colour with alcoholic ferric chloride, unaffected on dilution with water (Found: C, 56·3; H, 5·4; N, 14·8. $C_{13}H_{15}O_4N_3$ requires C, 56·3; H, 5·4; N, 15·2%).

Hydrolysis of 6-methoxy-3-acetyl-3 : 4-dihydrocoumarin (1 g.) with 0·5*N*-aqueous sodium hydroxide (20 ml.) on the steam-bath for 30 minutes gave the neutral 2-hydroxy-6-methoxy-2-methylchroman and the phenolic 2-hydroxy-5-methoxybenzylacetone, each of which furnished the 2 : 4-*dinitrophenylhydrazone* of 2-hydroxy-5-methoxybenzylacetone, forming scarlet rectangular prisms, m. p. 156°, from dilute alcohol (Found: C, 54·6; H, 5·0; N, 14·9. $C_{17}H_{16}O_8N_4$ requires C, 54·5; H, 4·8; N, 15·0%). When the coumarin was heated under reflux with *N*-alcoholic hydrochloric acid for 45 minutes the same mixed product was obtained, giving the 2 : 4-dinitrophenylhydrazone, m. p. 156°.

Oxidation of 6-*Methoxy*-3-*acetyl*-3 : 4-*dihydrocoumarin*.—(*a*) Dehydrogenation of 6-methoxy-3-acetyl-3 : 4-dihydrocoumarin (0·5 g.) in acetic acid (10 ml.) with lead tetra-acetate (1 g.) proceeded rapidly, giving 6-methoxy-3-acetylcoumarin, m. p. and mixed m. p. 182°, which formed the 2 : 4-dinitrophenylhydrazone, m. p. 242—243°.

(*b*) A slow stream of ozone and oxygen was led into a solution of the dihydrocoumarin (1 g.) in chloroform (75 ml.) maintained at 0° for 75 minutes, the solvent was removed in a vacuum, and the residue treated with water. Next day the water was decanted and on treatment with a little ether the residual oil gave crystalline 3-hydroxy-6-methoxycoumarin which separated from ethyl acetate in pale yellow prisms, m. p. 208—209°, giving an intense deep green ferric reaction in alcohol and identified by comparison with an authentic specimen. The ethereal filtrate from the crude 3-hydroxy-6-methoxycoumarin contained 2-hydroxy-5-methoxybenzaldehyde which was identified by conversion into the 2 : 4-*dinitrophenylhydrazone*, m. p. 263°, undepressed on admixture with an authentic sample (Found: N, 17·1. $C_{14}H_{12}O_6N_4$ requires N, 16·9%).

3-*Hydroxy*-6-*methoxycoumarin* (IX).—A mixture of 2-hydroxy-5-methoxybenzaldehyde (2 g.), aceturic acid (2·5 g.), acetic acid (3 ml.), acetic anhydride (10 ml.), and sodium acetate (1·6 g.) was heated on the steam-bath for 2 hours. The colourless crystalline product which separated from the cooled reaction mixture was removed, the residual liquor was diluted with water, and the yellow precipitate collected, washed with a little alcohol and then with ether to remove traces of resinous material. The crude azlactone (0·5 g.) was then boiled with 2*N*-hydrochloric acid (20 ml.) for 4 hours and the resulting 3-*hydroxy*-6-*methoxycoumarin* (0·3 g.) was isolated by filtration from the cooled reaction

mixture. Crystallised from alcohol (charcoal) and then from ethyl acetate, the compound formed pale fawn-coloured prisms, m. p. 208—210°, readily soluble in 1% aqueous sodium hydroxide and giving a characteristic deep-green ferric reaction (Found: C, 62·6; H, 4·3. $C_{18}H_8O_4$ requires C, 62·5; H, 4·2%).

Hydrogenation of 3-Acetyl-7-methylcoumarin.—This coumarin (Chuit and Bolsing, *Bull. Soc. chim.*, 1915, **35**, 84) formed a 2 : 4-*dinitrophenylhydrazone*, separating from acetic acid or ethyl acetate in masses of slender yellow needles, m. p. 225—226° (Found: N, 14·6. $C_{18}H_{14}O_6N_4$ requires N, 14·7%).

When the hydrogenation of the coumarin (2 g.) was effected by the procedure employed in the case of 6-methyl-3-acetylcoumarin the colourless product left on evaporation of the filtered reaction mixture had m. p. 80—90°, and gave a purple ferric reaction in alcohol. Crystallisation of this material several times alternately from aqueous methanol and benzene–ligroin and then from alcohol and benzene gave a *substance* in colourless prisms (1 g.), m. p. 129·5—130·5°, which was sparingly soluble in benzene and did not react with 2 : 4-dinitrophenylhydrazine or give a ferric reaction (Found: C, 70·8; H, 5·8. $C_{11}H_{12}O_2$ requires C, 70·6; H, 5·9%). This product dissolved slowly in hot 2*N*-aqueous sodium hydroxide and on acidification with dilute hydrochloric acid the original material, m. p. 128°, was obtained. It was not identical either with 7-methylcoumarin, m. p. 128° (the mixture of two compounds melted at 88—110°), or with 3-ethyl-7-methylcoumarin.

Treatment of the alcoholic mother-liquors left from the purification of the foregoing product with an excess of saturated copper acetate gave an amorphous green precipitate (1·2 g. from 3 g. of 3-acetyl-7-methylcoumarin) which, after having been washed with water, methanol, and then with ether, was decomposed with a mixture of 5% sulphuric acid and ether. Evaporation of the ethereal liquor gave *3-acetyl-7-methyl-3 : 4-dihydrocoumarin* which formed colourless platelets (0·56 g.), m. p. 95—97°, from dilute alcohol, readily soluble in the usual organic solvents except ligroin and giving a purple ferric reaction in alcohol (Found: C, 70·9; H, 5·8. $C_{11}H_{12}O_3$ requires C, 70·6; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in yellow needles, m. p. 190—192° (Found: C, 56·1; H, 4·2; N, 14·3. $C_{17}H_{16}O_6N_4$ requires C, 56·4; H, 4·2; N, 14·6%).

7-Methyl-3-ethylcoumarin was prepared by the butyrylation of 2-hydroxy-4-methylbenzaldehyde (3 g.) with butyric anhydride (5 g.) and sodium butyrate (5 g.) at 170° for 5hours and subsequent treatment of the reaction mixture with water. Crystallised from light petroleum (b. p. 60—80°), the coumarin (1·6 g.) formed colourless flat needles, m. p. 63—64°, soluble in alcohol or ethyl acetate (Found: C, 76·6; H, 6·6. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

7-Methoxy-3-acetylcoumarin.—Condensation of 4-*O*-methylresorcylaldehyde (6 g.) and ethyl acetoacetate (6 ml.) by means of a little piperidine gave rise to *7-methoxy-3-acetylcoumarin* which separated from ethyl acetate in pale yellow prisms (8 g.), m. p. 173—174° (Found: C, 66·0; H, 4·5. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%), showing in alcohol an intense blue fluorescence. Prepared by the pyridine method, the *oxime* formed almost colourless prisms, m. p. 217°, from alcohol and then ethyl acetate (Found: N, 5·6. $C_{12}H_{11}O_4N$ requires N, 6·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in tiny scarlet rhombs, m. p. 257—258° (decomp.) (Found: N, 14·1. $C_{18}H_{14}O_7N_4$ requires N, 14·1%).

Hydrogenation of 7-Methoxy-3-acetylcoumarin.—This coumarin (2 g.) was hydrogenated in methanol (300 ml.) with hydrogen at 60 lbs./sq. in. and palladium–charcoal (from 1 g. of charcoal and 0·3 g. of palladium chloride) during 2½ hours at room temperature. The colourless, filtered reaction mixture, which gave only a comparatively faint purple ferric reaction and only traces of a precipitate with 2 : 4-dinitrophenylhydrazine solution, was concentrated in a vacuum at below 50°, giving a crystalline solid (0·5 g.) which consisted mainly of *7-methoxy-3-ethylcoumarin*. Recrystallised from methanol and then ethyl acetate–ligroin, this compound formed colourless prisms, m. p. 98—100°, (Found: C, 70·1; H, 5·8. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%) undepressed on admixture with an authentic sample (cf. below).

Concentration of the liquor left after the separation of the crude 7-methoxy-3-ethylcoumarin furnished a solution which gave a purple ferric reaction and on treatment with an excess of aqueous copper acetate gave the copper derivative of *7-methoxy-3-acetyl-3 : 4-dihydrocoumarin*; the amount of this derivative obtained was variable, the maximum being 0·2 g. from 2 g. of 7-methoxy-3-acetylcoumarin. Decomposition of the crude copper compound was effected with 5% sulphuric acid (20 ml.) containing ether (20 ml.) (agitate) during 2 hours at room temperature, and the ethereal solution was separated, washed with aqueous sodium hydrogen carbonate, dried, and evaporated, leaving the dihydrocoumarin which formed colourless, elongated, flat prisms, m. p. 82·5—84·5°, from light petroleum (b. p. 60—80°) and gave an intense purple ferric reaction in alcohol (Found: C, 65·8; H, 5·4. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

An authentic specimen of 7-methoxy-3-ethylcoumarin was prepared by heating a mixture of 4-*O*-methylresorcylaldehyde (3 g.), sodium butyrate (6 g.), and butyric anhydride (6 g.) at 160° for 4 hours. The reaction mixture was boiled with water to decompose the excess of anhydride, cooled, and extracted with ether. Evaporation of the ethereal solution, which had been washed successively with *N*-aqueous sodium hydroxide and water and then dried, left a brown oil which partly solidified and on purification from methanol and then ethyl acetate–ligroin, gave 7-methoxy-3-ethylcoumarin in colourless prisms, m. p. 99—100°, soluble in alcohol, ethyl acetate, or chloroform (Found: C, 70·7; H, 6·0%).

Hydrogenation of 7-Hydroxy-3-acetylcoumarin.—This coumarin, m. p. 236°, was prepared by the condensation of β-resorcylaldehyde and ethyl acetate with a little pyridine (compare Weiss and Merksammer, *Monatsh.*, 1928, **50**, 115) and gave a 2 : 4-*dinitrophenylhydrazone*, forming scarlet needles, m. p. 302—303° (decomp.), from ethyl acetate (Found: N, 14·7. $C_{17}H_{12}O_7N_4$ requires N, 14·6%).

Hydrogenation of the coumarin (1 g.) by the procedure employed for its 7-methyl ether gave a tan-coloured crude product (1 g.), m. p. 70—100°, giving a faint violet ferric reaction in alcohol and forming, in dilute aqueous sodium hydroxide, a solution which had a brilliant blue fluorescence. A solution of this solid in a little hot alcohol was warmed with saturated aqueous sodium hydrogen sulphite (3 ml.) on the steam-bath for 15 minutes and on cooling the mixture deposited crystalline material

which was collected and again treated with warm alcohol and aqueous sodium hydrogen sulphite, finally giving 7-hydroxy-3-ethylcoumarin as a monohydrate in colourless shining needles, m. p. 128—129°, giving a negative ferric reaction (Fichter and Goldhaber, *Ber.*, 1904, **37**, 2382, record m. p. 123—124°) (Found: C, 63·2; H, 5·7. Calc. for $C_{11}H_{10}O_3,H_2O$: C, 63·5; H, 5·8%). Methylation of this compound by the potassium carbonate–methyl iodide method during 2 hours gave 7-methoxy-3-ethylcoumarin which separated from aqueous methanol in colourless prisms, m. p. 98—100°, undepressed on admixture with an authentic specimen.

Hydrogenation of **6**: 7-*Dimethoxy-3-acetylcoumarin.*—The *oxime* of this coumarin (Part II, *loc. cit.*) formed colourless slender needles, m. p. 218°, from alcohol (Found: N, 5·3. $C_{13}H_{13}O_5N$ requires N, 5·3%). The 2:4-dinitrophenylhydrazone had m. p. 282—283° (decomp.) and not 280° (decomp.) as given in Part II (*loc. cit.*).

Hydrogenation of the coumarin (2 g.) in methanol with palladium–charcoal and hydrogen at 60 lbs./sq. in. during 5—6 hours gave, after filtration, a colourless solution which gave a faint ferric reaction and became yellow on exposure to air.

Evaporation of the solution in an atmosphere of nitrogen, followed by extraction of the residue with a little hot methanol, left unchanged **6**: 7-dimethoxy-3-acetylcoumarin, m. p. 228°. On cooling, the methanolic extract deposited **6**: 7-*dimethoxy-3-ethylcoumarin* in pale yellow needles, m. p. 108—109°, identical with an authentic specimen (Found: C, 66·7; H, 5·9. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). The latter specimen was prepared by the butyrylation of 2-hydroxy-4:5-dimethoxybenzaldehyde with butyric anhydride and sodium butyrate at 170° for 6 hours and on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) was obtained in large prisms, m. p. 108—109° (Found: C, 66·6; H, 5·9%).

When a platinum–charcoal catalyst was employed in the hydrogenation and the product was subjected to prolonged fractional crystallisation in an atmosphere of nitrogen there was obtained, in addition to **6**: 7-dimethoxy-3-ethylcoumarin, a small amount of **6**: 7-*dimethoxy-3-acetyl*-**3**: 4-*dihydrocoumarin* (III; R = H). By treatment of several batches of filtered hydrogenation-liquor with an excess of aqueous copper acetate a small amount of the copper derivative of the latter coumarin was obtained which was washed with warm alcohol, chloroform, and ether and decomposed with dilute sulphuric acid and ether in the usual manner giving **6**: 7-dimethoxy-3-acetyl-**3**: 4-dihydrocoumarin, forming colourless prisms, m. p. 164—166°, from alcohol (Found: C, 62·2; H, 5·6. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). This compound was soluble in chloroform, ethyl acetate, benzene, or warm 1% aqueous sodium hydroxide and gave a purple ferric reaction in alcohol. Formed in the usual manner, the 2:4-dinitrophenylhydrazone was obtained as an orange yellow precipitate, m. p. 228°, which could not be satisfactorily recrystallised.

6-*Acetoacetyl*-**3**: 4-*dihydrocoumarin* (XI).—A solution of **3**: 4-dihydrocoumarin (3 g.) in acetic anhydride (8 ml.) at 0° was saturated with boron trifluoride (from 22 g. of potassium fluoroborate) and treated with ice-water 24 hours later. The boron fluoride complex of the diketone then slowly separated from the reaction mixture in pale yellow needles (2·3 g.), m. p. 120°. Decomposition of this (1 g.) with boiling water (3 ml.) containing hydrated sodium acetate (10 g.) during 10 minutes gave 6-acetoacetyl-**3**: 4-dihydrocoumarin, which was isolated from the cooled mixture with ether, purified by way of its copper derivative, and crystallised from ligroin or dilute alcohol, forming a hydrate in small colourless prisms (0·7 g.) giving a deep-red ferric reaction (Found: C, 62·3; H, 5·8. Calc. for $C_{13}H_{14}O_4,H_2O$: C, 62·4; H, 5·6%) (cf. Kacatnor, *loc. cit.*).

3-*Acetoacetylcoumarin* (XII; R = Ac).—A mixture of 3-acetylcoumarin (3 g.), acetic acid (10 ml.), and acetic anhydride (6 ml.) was saturated at room temperature with boron trifluoride, and ½ hour later the red viscous liquid was poured into water (50 ml.). Extraction of the washed, flocculent, orange-yellow product (3·7 g.) with alcohol removed viscous reddish impurities and left the boron fluoride complex of 3-acetoacetylcoumarin as a mass of orange crystals (2·3 g.), which, on recrystallisation from acetic acid formed yellow plates, m. p. 268°, sparingly soluble in organic solvents and giving a green flame test. On being heated on the steam-bath with acetic acid (50 ml.) and hydrated sodium acetate (2 g.) this compound (2·4 g.) slowly dissolved; after ½ hour water was added until the solution became faintly opalescent; 3-acetoacetylcoumarin (XII; R = Ac) separated from the cooled mixture in pale yellow prisms (1·5 g.), and, on recrystallisation from alcohol and then acetic acid, had m. p. 152—153° (Found: C, 67·5; H, 4·4. Calc. for $C_{13}H_{10}O_4$: C, 67·8; H, 4·4%). This compound, which gave a red ferric reaction in alcohol, was readily soluble in 2*N*-aqueous sodium hydroxide and insoluble in aqueous sodium carbonate. The 2:4-dinitrophenylhydrazone and the oxime were obtained as amorphous solids which could not be induced to crystallise (cf. Treninerowna, *Roczniki Chem.*, 1936, **16**, 6, 10, who states that the compound gives a blood-red ferric reaction and forms cream-yellow needles or blunt prisms, m. p. 143—144°).

Hydrogenation of this coumarin by the procedure employed for 3-acetylcoumarin gave a gummy product which was resolved by means of ether into unchanged 3-acetoacetylcoumarin and a small amount of a *substance* which formed elongated needle-shaped plates, m. p. 177—178°, from alcohol, giving a negative ferric reaction (Found: C, 67·1; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). It did not appear to react with 2:4-dinitrophenylhydrazine.

UNIVERSITY OF LIVERPOOL.

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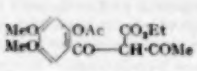
183. *The Chemistry of Fungi. Part X. The Synthesis of 4-Hydroxy-3-acetylcoumarins.*

By G. G. Badcock, F. M. Dean, Alexander Robertson, and W. B. Whalley.

Methods for the synthesis of 4-hydroxy-3-acetylcoumarins have been re-investigated and the novel synthetical procedures described in Part II (*loc. cit.*) have been further developed. It has been found that 4-hydroxycoumarins unsubstituted in the 3-position can be acetylated readily with acetic anhydride and boron trifluoride in acetic acid to give 4-hydroxy-3-acetylcoumarins, thus affording an unequivocal route to these interesting compounds. By this reaction the synthetic compound (Part II, *J.*, 1949, 562), m. p. 250°, has now been shown conclusively to be 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin. The hydrolysis product, m. p. 208°, from *O*-dimethylcitromycinone (Part III, *J.*, 1949, 848) has been found to have formula (XIV) and arises by the hydration of the parent compound (XV) which it regenerates on treatment with concentrated sulphuric acid.

In the course of degradative experiments on *O*-dimethylcitromycinone (Part III, *J.*, 1949, 848) there was isolated a faintly acidic substance, m. p. 208°, which was regarded as 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin (III) because it appeared to have the empirical formula $C_{11}H_6O_4(OMe)_2$, readily formed a 2 : 4-dinitrophenylhydrazone, and gave the requisite products on hydrolytic decomposition with alkalis. Unexpectedly, when the method of Anschütz (*Annalen*, 1906, **346**, 286) and the two novel procedures, *viz.*, the carbonyl chloride and the ethyl carbonate methods described in Part II (*J.*, 1949, 562), were applied to the synthesis of the coumarin (III) a product *P*, m. p. 250°, was invariably obtained which appeared not to react with 2 : 4-dinitrophenylhydrazine and was clearly not identical with the natural degradation product, m. p. 208°. From an examination of its properties and hydrolytic products, and in view of its apparent isomerism with the degradation product, m. p. 208°, the substance *P* was considered to be 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid (X; R = H). At the same time it was noted that the production of small amounts of 4-hydroxy-6 : 7-dimethoxycoumarin (IV) by the hydrolysis of *P* with alkalis was more in keeping with the 4-hydroxy-3-acetylcoumarin structure (III), but a plausible mechanism advanced for the derivation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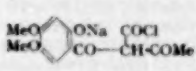
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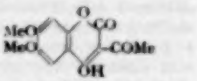
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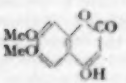
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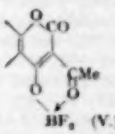
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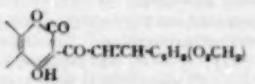
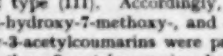

(VI.)

of 4-hydroxy-6 : 7-dimethoxycoumarin from (X; R = H) seemed to reconcile the apparent anomaly. Because of the possible ambiguity regarding the nature of the products obtained by the methods hitherto employed for the synthesis of 4-hydroxy-3-acetylcoumarins and since the substance, m. p. 208°, was regarded as an important hydrolytic product in the degradation series derived from *O*-dimethylcitromycinone, it seemed desirable to re-investigate the synthetical procedures and to examine the properties of 4-hydroxy-3-acetylcoumarins in some detail.

In our hands the procedure for the synthesis of 4-hydroxy-3-acetylcoumarins described by Anschütz (*loc. cit.*) gave somewhat uncertain results and a modified technique is now described whereby consistent yields of the required coumarins have been obtained. Of the novel alternative methods proposed in Part II (*loc. cit.*) the *o*-hydroxybenzoylacetone–ethyl carbonate method in the case of 2-*hydroxy*- and 2-*hydroxy*-5-*methyl-benzoylacetone* failed to yield the expected 4-hydroxy-3-acetylcoumarins, but with 2-hydroxy-4 : 5-dimethoxybenzoylacetone the results described in Part II (*loc. cit.*) were confirmed and a small yield of 4-hydroxy-3-acetyl-6 : 7-dimethoxycoumarin was invariably obtained. On the other hand, the carbonyl chloride method, *viz.*, the interaction of this reagent with the disodio-derivatives of *o*-hydroxybenzoylacetones, gave comparatively satisfactory yields of the requisite coumarins which were identical with the products obtained by the modified Anschütz method. It was recognised, however,

that in the latter procedure the initial reaction product, of type (I), might well undergo cyclisation to give a chromone of type (X; R = Et or R = H) in place of the expected coumarin of type (III), and that the carbonyl chloride method was open to the same objection, *e.g.*, the intermediate of type (II), if formed, could cyclise in two ways.

In a search for a more rational and general synthetical route to 4-hydroxy-3-acetylcoumarins it was ultimately discovered that 4-hydroxycoumarins, of type (IV), can be conveniently *C*-acetylated in the 3-position by means of acetic anhydride and boron trifluoride. From the initial reaction products water precipitated boron chelate complexes of type (V) which, on hydrolytic decomposition under the appropriate conditions (see Experimental section), furnished compounds of type (III). Accordingly, from 4-hydroxy-, 4-hydroxy-6-methyl-, 4-hydroxy-6-methoxy-, 4-hydroxy-7-methoxy-, and 4-hydroxy-6 : 7-dimethoxy-coumarin the corresponding 4-hydroxy-3-acetylcoumarins were prepared by this method and, except in the case of *4-hydroxy-6-methoxy-3-acetylcoumarin* where a comparison was not possible, the products were identical with those from the modified Anschütz and the carbonyl chloride procedures, a result which clearly eliminates the possibility of the compounds prepared by the latter methods being 2-methylchromone-3-carboxylic acids of type (X; R = H). Consequently the compound *P*, formulated in Part II (*loc. cit.*) as 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid is 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin, and its piperonylidene derivative is *4-hydroxy-6 : 7-dimethoxy-3-(3 : 4-methylenedioxycinnamoyl)coumarin* (VI) and not the 2-styryl derivative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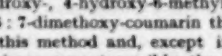
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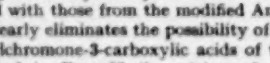
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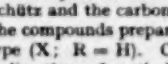
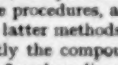

(X.)


(XI.)

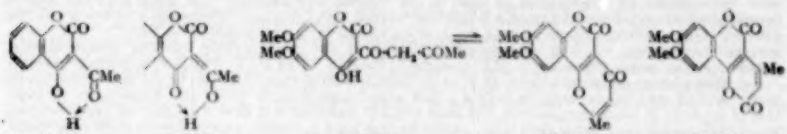
of the isomeric chromone. This conclusion has been substantiated by a synthesis of 6 : 7-*dimethoxy-2-methylchromone-3-carboxylic acid* (X; R = H). Condensation of 2-hydroxy-4 : 5-dimethoxyacetophenone with ethyl oxalate by means of sodium gave rise to *ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate* (VII; R = H), the nature of which was clarified by cyclisation with alcoholic hydrochloric acid to *ethyl 6 : 7-dimethoxychromone-2-carboxylate*. Hydrolysis of the chromone and decarboxylation of the resulting *acid* gave 6 : 7-dimethoxychromone. Vigorous acetylation of (VII; R = H) furnished a small amount of *ethyl 4 : 5-dimethoxy-2-methylchromone-3-glyoxylate* accompanied by considerable amounts of ethyl 6 : 7-dimethoxychromone-2-carboxylate. The same glyoxylate (IX) was also formed by the foregoing method when (VII; R = H) was replaced by the *acetate* (VII, R = Ac), and more conveniently when (VII, R = H) was cyclised with acetic anhydride and boron trifluoride at 0°, a reaction which clearly proceeds by way of the intermediate (VIII; R = H). On treatment with warm concentrated sulphuric acid the glyoxylate (IX) was hydrolysed with the simultaneous evolution of carbon monoxide, giving rise to 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid (X; R = H) which had the expected properties of a carboxylic acid and was readily differentiated from the isomeric 4-hydroxy-3-acetylcoumarin (III).

In the conversion of (VII; R = H or Ac) into (IX) by vigorous acetylation, a reaction which presumably proceeds by way of (VIII), cyclisation of this intermediate could lead, by an alternative route, to *ethyl 6 : 7-dimethoxy-3-acetylchromone-2-carboxylate* (XI; R = Et). Although with (VII; R = H) as the starting material ethyl 6 : 7-dimethoxy-3-acetylchromone-2-carboxylate (XI; R = Et) could not be isolated, the acetate (VII; R = Ac) gave a small amount of (XI; R = Et) which accompanied the main reaction product (IX). This compound (XI; R = Et) is readily distinguished from the isomeric ethyl 4 : 5-dimethoxy-2-methylchromone-3-glyoxylate by the fact that unlike the latter it does not evolve carbon monoxide on being heated with sulphuric acid and on hydrolysis with concentrated acid gave 6 : 7-*dimethoxy-3-acetylchromone-2-carboxylic acid* (XI; R = H).

The 4-hydroxy-3-acetylcoumarins described in the present work melt without decomposition and are readily soluble in dilute aqueous sodium hydroxide. Unlike the parent 4-hydroxycoumarins, however, they dissolve but slowly in aqueous sodium hydrogen carbonate and apparently cannot be readily methylated or acetylated under the usual conditions, although it may be noted that Anschütz (*loc. cit.*) claims to have prepared a methyl ether of 4-hydroxy-

3-acetyl-7-methylcoumarin. With 2 : 4-dinitrophenylhydrazine sulphate solution 4-hydroxy-, 4-hydroxy-6-methyl-, and 4-hydroxy-7-methoxy-3-acetyl-coumarin reacted readily under the usual conditions, yielding the corresponding 2 : 4-dinitrophenylhydrazones, but 4-hydroxy-6-methoxy-3-acetylcoumarin reacted extremely slowly, whilst, as indicated in Part II (*loc. cit.*), 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin did not form a dinitrophenylhydrazone. Treatment of the 4-hydroxy-3-acetylcoumarins with warm 80% sulphuric acid caused extrusion of the *C*-acetyl group and gave rise to the corresponding 4-hydroxycoumarins.

The properties of 4-hydroxy-3-acetylcoumarins are in keeping with the view that the molecule contains a hydrogen-bonded system involving a comparatively stable 6-atom ring of which the two formulæ (XII) and (XIII) represent the unperturbed forms of the resonating system. Substituents in the benzenoid ring appear to affect materially the stability of the chelate system.



(XII.) (XIII.) (XIV.) (XV.) (XVI.)

When it became clear that the hydrolytic product, m. p. 208°, from *O*-dimethylcitromycinone could not be 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin (III), a re-examination of the compound was undertaken. The analytical results do not materially differ from the theoretical values required for (III) or for a *C*-acetyl derivative of this coumarin. On this account, combined with the fact that unlike (III) it readily formed a 2 : 4-dinitrophenylhydrazone, we concluded that the compound, m. p. 208°, was *4-hydroxy-6 : 7-dimethoxy-3-acetoacetylcoumarin* (XIV) which was confirmed when it was found that cyclisation with warm sulphuric acid regenerated *O*-dimethylcitromycinone, identical with the product obtained by the oxidation of *O*-dimethylcitromycin. Since, in the conversion of (XIV) into *O*-dimethylcitromycinone, it is reasonably certain that the readily enolisable 4-carbonyl group (the 4-hydroxyl group of the coumarin system) was involved in the cyclisation and not the more stable carbonyl group of the lactone system, *O*-dimethylcitromycinone has the angular structure (XV) and not the linear formula proposed in Part III (*loc. cit.*). Mr. G. W. K. Cavill of this Department (private communication), who has examined the decomposition of *O*-dimethylcitromycinol (Part III, *loc. cit.*), has independently concluded that *O*-dimethylcitromycin as well as the primary oxidation products have angular structures corresponding to (XV), possibilities which were envisaged but not supported in Part III. Detailed experimental evidence in support of this revised structure for *O*-dimethylcitromycin and its derivatives will be discussed in a subsequent communication.

During numerous exploratory experiments on the synthesis of the diketone (XIV) and hence of *O*-dimethylcitromycinone (XV) it was found that 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin could not be *C*-acetylated to give (XIV) [or its cyclisation product (XV)] by boron trifluoride-acetic anhydride, the Claisen reaction, or the Kostanecki vigorous-acetylation process. The alternative route of forming the γ-pyrone ring in (XV) by the condensation of acetoacetic acid or its ester with 4-hydroxy-6 : 7-dimethoxycoumarin was attempted but, as expected, with the usual condensing agents (concentrated sulphuric acid, phosphoric oxide, or phosphorus oxychloride) this reaction gave only 6 : 7-*dimethoxy-4'-methyl-α-pyrono*(5' : 6' : 3 : 4)*coumarin* (XVI) isomeric with *O*-dimethylcitromycinone. The failure of (XVI) to dissolve in concentrated hydrochloric acid or to form salts, and its behaviour with dilute aqueous sodium hydroxide, is in keeping with the α-pyrono-coumarin structure and readily serves to distinguish the compound from *O*-dimethylcitromycinone.

Experimental.

4-Hydroxy-3-acetylcoumarin.—(*a*) Ethyl acetoacetate (3·8 ml.), dissolved in ether (20 ml.), was added to ethereal sodium ethoxide (from 0·7 g. of sodium, 5 ml. of alcohol, and 20 ml. of ether), followed by a solution of *o*-acetoxybenzoyl chloride (from 5 g. of acid) in ether (10 ml.), and the mixture warmed under reflux for 1 hour. More sodium ethoxide (from 0·7 g. of sodium) in a mixture of alcohol and ether (10 ml.) was added to the reaction mixture which became yellow and then deposited a yellow precipitate. The reaction was completed by warming the mixture for a further 3 hours and on isolation the solid was washed with ether, dried, and dissolved in water (150 ml.). Acidification of this solution with concentrated hydochloric acid gave 4-hydroxy-3-acetylcoumarin (2·9 g.) which formed needles, m. p. 138·5°, from alcohol (cf. Anschütz, *Annalen*, 1909, **367**, 194, who gives m. p. 134°).

(*b*) After the initial reaction between *o*-hydroxyacetophenone (5 g.), pulverised sodium (4 g.), and ethyl acetate (30 ml.) had somewhat subsided the mixture was heated on the water-bath for ½ hour, cooled, and treated with crushed ice (25 g.). The sodio-derivative of salicyloylacetone, which separated, was collected, washed with a little ice-water and then ether, and decomposed with dilute acetic acid, giving the diketone (3·2 g.) which formed square colourless prisms from alcohol, or plates, m. p. 95°, from light petroleum, and had a reddish-brown ferric reaction in alcohol (Found : C, 67·2; H, 5·6. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·7%) (Wittig, Bangert, and Richter, *Annalen*, 1926, **446**, 155, record m. p. 90·5—91·5°). Cyclisation of this ketone with sulphuric acid gave an almost theoretical yield of 2-methylchromone, m. p. 71° (Block and Kostanecki, *Ber.*, 1900, **33**, 1909, give m. p. 70—71°).

The foregoing diketone (5 g.) was added to a solution of sodium ethoxide (from 1·6 g. of sodium) in alcohol (30 ml.), the greater part of the solvent was distilled in a vacuum, and the disodio-derivative was precipitated from the cooled residue by means of ether (200 ml.), washed and dried (yield, 6·4 g. of a lemon-yellow powder). A slow stream of carbonyl chloride was led into a suspension of this derivative (5 g.) in toluene (75 ml.) cooled with ice-salt. The liquid became scarlet and next day the mixture was filtered, the sodium chloride was washed with a little toluene, and the combined filtrate and washings were concentrated by evaporation of most of the toluene in a vacuum. On being kept the residue deposited 4-hydroxy-3-acetylcoumarin which was washed with ether and obtained as a yellow crystalline powder (0·7 g.). Purified from alcohol, the compound had m. p. and mixed m. p. 138·5°. The 2 : 4-*dinitrophenylhydrazone*, which is very sparingly soluble in the usual organic solvents, separated from nitrobenzene in orange plates, m. p. 271° (decomp.) (Found : N, 14·9. $C_{17}H_{12}O_7N_4$ requires N, 14·6%).

(*c*) When boron trifluoride (from 22 g. of potassium fluoroborate) was slowly led into a mixture of acetic acid (5 ml.), acetic anhydride (2 g.), and 4-hydroxycoumarin (Boyd and Robertson, *J.*, 1948, 174) (1 g.) kept at room temperature, the solid quickly dissolved and next day the pale yellow viscous liquid was poured into water (100 ml.). After having been collected, thoroughly washed with water, and dried, the resulting fawn-coloured crystalline precipitate (1·2 g.) was decomposed with boiling 95% alcohol (50 ml.), and on cooling the mixture deposited 4-hydroxy-3-acetylcoumarin in long needles, m. p. and mixed m. p. 138°, identical with specimens prepared by methods (*a*) and (*b*). This coumarin dissolves slowly in aqueous sodium hydrogen carbonate and gives a yellow colour with alcoholic ferric chloride which becomes orange when the mixture is warmed. The 2 : 4-dinitrophenylhydrazone formed orange leaflets, m. p. and mixed m. p. 271° (decomp.), from nitrobenzene.

A mixture of 4-hydroxy-3-acetylcoumarin (0·2 g.), alcoholic sodium ethoxide (from 0·03 g. of sodium and 10 ml. of alcohol), and piperonal (0·15 g.) was warmed on the steam-bath for 30 minutes and the cooled orange reaction mixture poured into 2*N*-hydrochloric acid (20 ml.). Crystallisation of the resulting precipitate from acetic acid gave the *piperonylidene* derivative in orange needles (0·18 g.), m. p. 252° after sintering at 248° (Found : C, 67·6; H, 3·8. $C_{19}H_{12}O_6$ requires C, 67·9; H, 3·6%).

4-*Hydroxy*-3-*acetyl*-6-*methylcoumarin*.—(*a*) Prepared by the modification of Anschütz and Sieber's method (*Annalen*, 1909, **367**, 250) employed for the preparation of 4-hydroxy-3-acetylcoumarin, 4-hydroxy-3-acetyl-6-methylcoumarin had m. p. 147·5°, and gave a yellow ferric reaction in alcohol; yield, 1·7 g. from 5 g. of 2-acetoxy-5-methylbenzoyl chloride (Found : C, 66·0; H, 4·6. Calc. for $C_{12}H_{10}O_4$: C, 66·0; H, 4·6%).

(*b*) Interaction of the disodio-derivative of 2-hydroxy-5-methylbenzoylacetone (Baker, *J.*, 1933, 1381) (5 g.) with excess of carbonyl chloride in toluene (75 ml.) gave rise to 4-hydroxy-3-acetyl-6-methylcoumarin (0·7 g.), m. p. and mixed m. p. 147·5°. The 2 : 4-*dinitrophenylhydrazone* formed clusters of orange needles from nitrobenzene or orange prisms, m. p. 265° (decomp.), from acetic acid (Found : N, 14·5. $C_{18}H_{14}O_7N_4$ requires N, 14·1%).

(*c*) The boron complex, m. p. 228° (decomp.), formed by the interaction of 4-hydroxy-6-methylcoumarin (Boyd and Robertson, *loc. cit.*) (1 g.), acetic acid (3 ml.), acetic anhydride (2 g.), and excess of boron trifluoride, was dissolved in boiling alcohol. On cooling, the solution deposited 4-hydroxy-3-acetyl-6-methylcoumarin as a mixture of rods and diamond-shaped prisms (0·9 g.), m. p. 148° after slight sintering at 140°, unchanged on further purification (Found : C, 66·1; H, 4·6%). The 2 : 4-dinitrophenylhydrazone had m. p. 264° (decomp.). Prepared by the method employed in the case of 4-hydroxy-3-acetylcoumarin, the *piperonylidene* derivative from 4-hydroxy-6-methyl-3-acetylcoumarin (0·2 g.) formed small orange needles (0·19 g.), m. p. 260—261°, from acetic acid and gave a violet colour with concentrated sulphuric acid (Found : C, 68·4; H, 4·1. $C_{20}H_{14}O_6$ requires C, 68·6; H, 4·0%).

4-*Hydroxy*-7-*methoxy*-3-*acetylcoumarin*.—(*a*) This *coumarin* (2·6 g.) was prepared from 2-hydroxy-4-methoxybenzoyl chloride (from 6·5 g. of acid) by the modified Anschütz method and on crystallisation from alcohol and then ethyl acetate–light petroleum (b. p. 80—100°) was obtained in yellowish-cream-coloured needles, m. p. 187·5°, giving a golden-yellow ferric reaction in alcohol which became red on warming (Found : C, 61·5; H, 4·7. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%).

(*b*) Interaction of the disodio-derivative of 2-hydroxy-4-methoxybenzoylacetone (Kostanecki and Lloyd, *Ber.*, 1901, **34**, 2942) (2·5 g.) with excess of carbonyl chloride in toluene (40 ml.) during 24 hours furnished 4-hydroxy-7-methoxy-3-acetylcoumarin (1·1 g.), m. p. 187·5°, after purification from alcohol. The 2 : 4-*dinitrophenylhydrazone* formed small red needles, m. p. 255°, from nitrobenzene (Found : N, 13·8. $C_{18}H_{14}O_8N_4$ requires N, 13·5%). When subjected to the standard method for the preparation of a piperonylidene derivative, almost all the 4-hydroxy-7-methoxy-3-acetylcoumarin was recovered unchanged.

(*c*) 4-*Acetoxy*-7-*methoxycoumarin* was prepared by the acetylation of 4-hydroxy-7-methoxycoumarin (Boyd and Robertson, *loc. cit.*) (4 g.) with hot acetic anhydride (40 ml.) during 1 hour and on isolation crystallised from alcohol in flat needles (4 g.), m. p. 133—134°, insoluble in aqueous sodium hydrogen carbonate (Found : C, 61·7; H, 4·5. $C_{13}H_{12}O_5$ requires C, 61·5; H, 4·3%). Interaction of the acetate (1 g.) with acetic acid (3 ml.), acetic anhydride (2 g.), and excess of boron trifluoride was accompanied by deacetylation and gave 4-hydroxy-7-methoxy-3-acetylcoumarin, m. p. 189, identical with specimens prepared by methods (*a*) and (*b*) (Found : C, 61·1; H, 4·4%). The 2 : 4-dinitrophenylhydrazone had m. p. 262° (decomp.) after sintering at 255°.

4-*Hydroxy*-6-*methoxycoumarin*.—When the vigorous reaction (initiated by gentle warming) between

2-hydroxy-5-methoxyacetophenone (Kostanecki and Lampe, *Ber.*, 1904, **37**, 774) (1·4 g.), ethyl carbonate (20 ml.), and pulverised sodium (0·4 g.) had somewhat subsided, the mixture was heated on the steam-bath for 1 hour, cooled, treated with a little methanol, and diluted with much ether. On isolation the solid was washed with ether and decomposed with excess of dilute hydrochloric acid, giving *4-hydroxy-6-methoxycoumarin* which formed colourless needles (1·6 g.), m. p. 179° (decomp.), from dilute alcohol, soluble in aqueous sodium hydrogen carbonate (Found: C, 62·5; H, 4·2. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%).

4-Hydroxy-6-methoxy-3-acetylcoumarin.—Interaction of the foregoing coumarin (0·7 g.), acetic acid (6 ml.), acetic anhydride (1·4 g.), and excess of boron trifluoride in the usual manner gave a solid (0·8 g.), m. p. ~180°, which on being dissolved in boiling alcohol yielded *4-hydroxy-6-methoxy-3-acetylcoumarin*. This compound separated from the cooled solution in long silky needles, changing to small prisms when left in contact with the solvent and, on recrystallisation from acetic acid, formed elongated rectangular prisms, m. p. 153°, slowly soluble in aqueous sodium hydrogen carbonate and giving an orange-yellow ferric reaction in alcohol (Found: C, 61·2; H, 4·5. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). Prepared under the usual conditions, the 2 : *4-dinitrophenylhydrazone* was very slowly formed and after being extracted with boiling alcohol the crude product crystallised from nitrobenzene in orange rectangular plates, m. p. 246—247° (Found: C, 52·5; H, 3·6. $C_{18}H_{14}O_8N_4$ requires C, 52·2; H, 3·4%).

4-Hydroxy-6 : 7-dimethoxy-3-acetylcoumarin (III).—(*a*) The interaction of 2-acetoxy-4 : 5-dimethoxybenzoyl chloride [from 5 g. of 2-acetoxy-4 : 5-dimethoxybenzoic acid (Head and Robertson, *J.*, 1931, 2432)], and ethyl sodioacetoacetate (from 3 ml. of ester and 0·52 g. of sodium) in ether (20 ml.), followed by treatment of the mixture with warm alcoholic sodium ethoxide (from 0·52 g. of sodium and 15 ml. of alcohol) in ether (50 ml.) on the water-bath for 3 hours, gave *4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin* which separated from alcohol in lemon-yellow needles, m. p. 250° (Found: C, 59·7; H, 4·6. $C_{13}H_{12}O_5$ requires C, 59·1; H, 4·6%).

(*b*) The foregoing coumarin was formed by the action of excess of carbonyl chloride on the disodio-derivative of 2-hydroxy-4 : 5-dimethoxybenzoylacetone (Part II, *loc. cit.*) in toluene cooled in an ice-salt bath during 24 hours. The product formed pale yellow needles (1·5 g.), m. p. and mixed m. p. 250°.

(*c*) Obtained by the interaction of 4-hydroxy-6 : 7-dimethoxycoumarin (1 g.), acetic anhydride (2 g.), and excess of boron trifluoride in acetic acid (5 ml.), the viscous reaction mixture was treated with water (50 ml.), and the bright yellow precipitate (1·1 g.) isolated, washed, and dried. On being cooled a solution of the product in hot acetic acid deposited the unchanged boron complex in yellow needles, m. p. 280°, insoluble in cold 2*N*-aqueous sodium hydroxide and giving a green flame test. When this compound was boiled with 50% aqueous sodium acetate or with sodium acetate in acetic acid, a colourless solution was slowly formed which, on being cooled, deposited 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin in cream-coloured needles (0·8 g.), m. p. and mixed m. p. 250°. This compound, which gave a golden-yellow colour with ferric chloride in alcohol and slowly dissolved in aqueous sodium hydrogen carbonate, did not appear to form a 2 : 4-dinitrophenylhydrazone.

Ethyl 2-Hydroxy-4 : 5-dimethoxybenzoylpyruvate (VII; R = H).—When a well agitated mixture of 2-hydroxy-4 : 5-dimethoxyacetophenone (Part II, *loc. cit.*) (5 g.), ethyl oxalate (15 ml.), and pulverised sodium (0·8 g.), containing one drop of alcohol, was heated on the steam-bath, a vigorous reaction ensued and the reaction mixture set to a stiff paste. After the addition of sufficient methanol to destroy unchanged sodium, followed by an excess of ether, the sodio-derivative was collected, washed with ether, mixed with acetic acid (10 ml.), and then treated with a considerable volume of water. Thus precipitated, *ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate* was collected and crystallised from aqueous alcohol, forming small yellow needles (4·9 g.), m. p. 157°, which give an olive-green, amber-tinged ferric reaction in alcohol (Found: C, 56·9; H, 5·6. $C_{13}H_{14}O_7$ requires C, 56·7; H, 5·4%).

A solution of this ester (3 g.) in pyridine (7 ml.) and acetic anhydride (10 ml.) was kept at room temperature for 18 hours and then mixed with an excess of dilute hydrochloric acid, giving a viscous precipitate which slowly solidified. Crystallised from alcohol this gave *ethyl 2-acetoxy-4 : 5-dimethoxybenzoylpyruvate* (VII; R = Ac) in pale lemon-yellow, feathery needles (2 g.), m. p. 133°, exhibiting a reddish-brown ferric reaction in alcohol (Found: C, 56·9; H, 5·4. $C_{15}H_{16}O_8$ requires C, 56·6; H, 5·3%).

A solution of ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate (1 g.) in the minimum quantity of warm acetic acid was treated with a drop of concentrated hydrochloric acid, heated on the steam-bath for 15 minutes, and then poured on ice, giving a precipitate of *ethyl 6 : 7-dimethoxychromone-2-carboxylate* which, on crystallisation from alcohol or ethyl acetate–light petroleum (b. p. 60—80°), formed tiny, cream-coloured needles (0·88 g.), m. p. 182° (Found: C, 60·2; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·2; H, 5·1%). When a solution of this chromone-ester (5 g.) in hot alcohol (50 ml.) was mixed with concentrated hydrochloric acid (25 ml.) and then heated under reflux for 3 hours 6 : 7-*dimethoxychromone-2-carboxylic acid* gradually separated. On isolation from the cooled mixture, this compound was purified by crystallisation from hot nitrobenzene and obtained in tiny, pale cream-coloured needles (3·5 g.), m. p. 303° (decomp.), readily soluble in cold aqueous sodium hydrogen carbonate and insoluble in the usual organic solvents (Found: C, 57·6; H, 4·2. $C_{12}H_{10}O_6$ requires C, 57·6; H, 4·0%). On being heated above its melting point this acid (1 g.) readily evolved carbon dioxide, leaving a residue of 6 : 7-dimethoxychromone which was purified by sublimation in a high vacuum at 180° and obtained in small irregular, almost colourless prisms (0·6 g.), m. p. 163°, from light petroleum (b. p. 60—80°), identical with an authentic specimen (Part II, *loc. cit.*).

Ethyl 2-Methyl-6 : 7-dimethoxychromone-3-glyoxylate (IX).—(*a*) A mixture of ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate (6 g.), sodium acetate (6 g.), and acetic anhydride (30 ml.) was heated on the steam-bath for 15 minutes, treated with water (100 ml.), and then warmed until a clear solution was obtained. On being kept at 0° the reaction mixture slowly deposited ethyl 6 : 7-dimethoxychromone-2-carboxylate (3·2 g.) and, after the separation of the latter, the liquor on the addition of water (200 ml. and then 300 ml.) deposited more ethyl 6 : 7-dimethoxychromone-2-carboxylate (0·5 g.), followed by *ethyl 6 : 7-dimethoxy-2-methylchromone-3-glyoxylate* (IX) (*ca.* 0·5 g.). Although the glyoxylate separated in this manner in two experiments, in a number of cases it failed to do so and was isolated from the

diluted liquor by extraction with ethyl acetate. Repeated crystallisation of the crude glyoxylate from alcohol, benzene–light petroleum (b. p. 60—80°), and finally ethyl acetate gave the compound in almost colourless tiny needles, m. p. 182°, which on admixture with ethyl **6** : 7-dimethoxychromone-2-carboxylate had m. p. ~160° (Found : C, 59·8; H, 4·9. $C_{14}H_{14}O_7$ requires C, 60·0; H, 5·0%). The *semicarbazone* separated from water in small colourless prisms, m. p. 240° (decomp.) (Found : N, 10·7. $C_{15}H_{17}O_7N_3$ requires N, 11·1%).

(*b*) A mixture of ethyl 2-hydroxy-**4** : 5-dimethoxybenzoylpyruvate (**3** g.), acetic anhydride (11 ml.), and acetic acid (5 ml.) was saturated at 0° with boron trifluoride, and 24 hours later the orange-red complex was collected, washed with acetic acid, and warmed with acetic acid (17 ml.), water (7 ml.), and sodium acetate (7 g.). The resulting homogeneous solution was then diluted with water (250 ml.), and next day the gummy semi-crystalline product was collected and purified by crystallisation as in method (*a*), giving a small yield of ethyl **6** : 7-dimethoxy-2-methylchromone-3-glyoxylate, m. p. and mixed m. p. 182°.

(*c*) When a mixture of ethyl 2-acetoxy-**4** : 5-dimethoxybenzoylpyruvate (2 g.), sodium acetate (2 g.), and acetic anhydride (10 ml.) was warmed on the steam-bath for 5 minutes and diluted with water (150 ml.), a semi-crystalline solid (2 g.) separated which, on repeated purification from alcohol, benzene, and ethyl acetate, gave a small yield of ethyl **6** : 7-dimethoxy-2-methylchromone-3-glyoxylate, m. p. and mixed m. p. 182°.

Evaporation of the mother-liquors from the purification of the foregoing chromone-3-glyoxylate prepared by method (*c*), followed by slow crystallisation of the residue from ethyl acetate, gave *ethyl* **6** : 7-*dimethoxy*-3-*acetylchromone*-2-*carboxylate* (XI ; R = Et) in thick, massive, colourless prisms (0·5 g.), m. p. 147°, after repeated purification (Found : C, 60·0; H, 5·0%). This compound (0·2 g.), which had a negative ferric reaction, was warmed on the steam-bath with concentrated sulphuric acid (3 ml.) for 5 minutes, the solution was treated with crushed ice, and the resulting precipitate was isolated by extraction with much chloroform. Crystallisation of the product from the same solvent yielded **6** : 7-*dimethoxy*-3-*acetylchromone*-2-*carboxylic acid* (XI ; R = H) in colourless prisms (0·15 g.), m. p. 240—241° (decomp.), sparingly soluble in alcohol or chloroform, almost insoluble in benzene or light petroleum, readily soluble in 2N-aqueous sodium hydrogen carbonate (Found : C, 57·4; H, 4·2. $C_{14}H_{12}O_7$ requires C, 57·5; H, 4·1%). Decarboxylation of this acid appeared to give a mixture of non-acidic compounds which was not further investigated.

When heated on the steam-bath with concentrated sulphuric acid (5 ml.), ethyl **6** : 7-dimethoxy-2-methylchromone-3-glyoxylate (0·5 g.) evolved carbon monoxide and, after the effervescence had ceased, the reaction mixture was treated with ice. Crystallisation of the resulting precipitate from acetic acid (charcoal) or from chloroform–light petroleum (b. p. 60—80°) gave **6** : 7-*dimethoxy*-2-*methylchromone*-3-*carboxylic acid* in tiny colourless needles (0·38 g.), m. p. 224° (decomp.) (Found : C, 59·0; H, 4·5. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%).

[With G. W. K. Cavill.] **4**-*Hydroxy*-**6** : 7-*dimethoxy*-3-*acetoacetylcoumarin* (XIV).—A solution of *O*-dimethylcitromycinone (Part III, *loc. cit.*) (1 g.) in concentrated hydrochloric acid (50 ml.) was heated on the steam-bath for 10 minutes, diluted with water (100 ml.), almost neutralised with 2N-aqueous sodium hydroxide, and extracted with ether (50 ml. × 5). During the extraction unchanged *O*-dimethylcitromycinone (0·8 g.), which is insoluble in ether, separated from the aqueous liquor. Evaporation of the dried ethereal extract left **4**-*hydroxy*-**6** : 7-*dimethoxy*-3-*acetoacetylcoumarin* which formed colourless needles (0·05 g.), m. p. 208° (decomp.), from ethanol (Found : C, 58·8; H, 4·7. $C_{13}H_{14}O_7$ requires C, 58·8; H, 4·6%).

The yellow solution of the compound (0·04 g.) in concentrated sulphuric acid (2 ml.) was kept at room temperature for 24 hours and then poured into ice-water (30 ml.). The pale yellow solid, which slowly separated, was collected, well washed, and crystallised from acetic acid, giving *O*-dimethylcitromycinone in colourless prisms (0·02 g.), m. p. 314—316° (decomp.), undepressed on admixture with an authentic specimen.

6 : 7-*Dimethoxy*-**4**′-*methyl*-*α*-*pyrono*(5′ : 6′ : 3 : 4)*coumarin* (XVI).—A mixture of **4**-hydroxy-**6** : 7-dimethoxycoumarin (1 g.), phosphoric oxide (**4** g.), ethyl acetoacetate (2 ml.), and acetic acid (20 ml.) was heated on the steam-bath for 20 minutes and the resulting brownish semi-solid was transferred portion-wise to an excess of water. After having been well washed with aqueous sodium hydrogen carbonate and water the resulting crystalline product was extracted with concentrated hydrochloric acid and then recrystallised from acetic acid (charcoal), giving the *α-pyrono-coumarin* in pale cream-coloured, thin prisms (0·9 g.), m. p. 292° (slight decomp.) [Found : C, 62·6; H, 4·3; OMe, 21·7. $C_{15}H_8O_4(OMe)_2$ requires C, 62·5; H, 4·2; OMe, 21·5%]. This compound dissolves slowly in hot 2N-aqueous sodium hydroxide and is precipitated unchanged on acidification of the yellow alkaline solution with dilute hydrochloric acid. An acetic acid solution of the coumarin exhibits an intense purple fluorescence.

When the phosphoric oxide was replaced by phosphorus oxychloride in the foregoing reaction the yield of coumarin was 0·35 g., whilst with concentrated sulphuric acid only a very small amount of the compound was formed.

University of Liverpool.

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184. 1 : 4-*Oxazines. Part I. Synthesis of Hydroxy*-1 : 4-*oxazines.*

By G. T. Newbold, F. S. Spring, and Wilfred Sweeny.

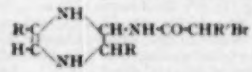
A simple method for the synthesis of 1 : 4-oxazine derivatives is described in which an α-bromoacyl derivative (VII) of ethyl α-amino-β-ketobutyrate is treated with ammonia or sodium ethoxide. In this way, ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate (VIII; R = Me, R′ = Et) and ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate (VIII; R = H, R′ = Et) have been prepared. The esters can be hydrolysed to the corresponding acids (VIII; R′ = H) which when heated lose carbon dioxide to yield the hydroxy-1 : 4-oxazines (IX).

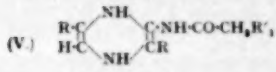
Treatment of an α-bromoacyl derivative (I) of an α-amino-ketone of the type NH_2·CHR·COR′ (in which R is not hydrogen) with ammonia gives a hydroxypyrazine (II) (Tota and Elderfield, *J. Org. Chem.*, **1942**, **7**, 317; Newbold and Spring, *J.*, **1947**, 373). Similar treatment of an α-bromoacyl derivative (III) of an aminomethyl ketone, however, gives a 2-acylamidopyrazine (VI) (Newbold, Spring, and Sweeny, *J.*, **1948**, 1855; **1949**, 300). The mechanism proposed for the latter reaction involves the self-condensation of the aminomethyl ketone derivative (III) to give a tetrahydropyrazine (IV) which is converted by an intramolecular reductive dehalogenation into a dihydropyrazine such as (V), oxidation of which gives the aromatic pyrazine (VI). This mechanism is in accord with the observation that this type of reaction only takes place with aminomethyl ketone derivatives and that it requires the presence of a halogen substituent in the acyl group. Furthermore, in one instance the dihydropyrazine intermediate was sufficiently stable to allow its isolation.

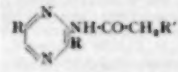
(I.) R′·CO·CHR·NH·CO·CHR″Br

R·CO·CH_2·NH·CO·CHR′Br (III.)

(II.)

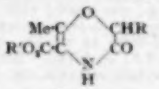

(IV.)

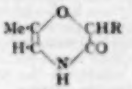

(V.)


(VI.)

Me·CO·CH(CO_2Et)·NH·CO·CHRBr

(VII.)


(VIII.)


(IX.)

Since Tota and Elderfield's direct method could not be applied to the synthesis of 3 : 5-disubstituted 2-hydroxypyrazines, an examination was made of the action of ammonia on an α-bromoacyl derivative of type (I) in which R is a group capable of elimination after ring-closure is complete; the object of this approach was to enforce 2-hydroxypyrazine formation and exclude 2-acylamidopyrazine formation by temporary protection of the methylene group essential for the latter reaction. The present paper records our experience with α-bromoacyl derivatives (VII) of ethyl α-amino-β-ketobutyrate (ethyl α-aminoacetoacetate).

Acylation of this ester with α-bromopropionyl chloride in the presence of *N*-methylmorpholine gives ethyl α-(α-bromopropionamido)-β-ketobutyrate (VII; R = Me). Treatment of the last compound with liquid ammonia at room temperature gives neither a hydroxypyrazine nor an acylamidopyrazine but a 1 : 4-oxazine derivative, ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate (VIII; R = Me, R′ = Et) by simple elimination of the elements of hydrogen bromide. This 1 : 4-oxazine derivative is more conveniently obtained by treatment of (VII; R = Me) with sodium ethoxide. Cautious alkaline hydrolysis of ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate gives the corresponding 1 : 4-oxazine-3-carboxylic acid (VIII; R = Me, R′ = H) which when heated yields 3-hydroxy-2 : 6-dimethyl-1 : 4-oxazine (IX; R = Me).

In a similar manner treatment of ethyl α-bromoacetamido-β-ketobutyrate (VII; R = H) with ammonia or, better, sodium ethoxide yields ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate (VIII; R = H, R′ = Et), hydrolysed to 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylic acid (VIII; R = R′ = H) from which 5-hydroxy-2-methyl-1 : 4-oxazine (IX; R = H) is obtained by the action of heat.

Although tetrahydro-1 : 4-oxazines (morpholines) are well known, as are compounds such as

phenoxazine containing the 1 : 4-oxazine system as part of a fused aromatic ring system, as far as we are aware simple 1 : 4-oxazine derivatives have not previously been described; Hill and Powell (*J. Amer. Chem. Soc.*, 1945, **67**, 1462) have suggested that a dehydration product from a benzoyl derivative of 3 : 4-dihydroxyphenacylaminoethanol is a dihydro-1 : 4-oxazine, and Cook and Cox (*J.*, 1949, 2347; cf. Chadwick and Pacsu, *J. Amer. Chem. Soc.*, 1943, **65**, 392) have described a series of 2 : 5-diketomorpholines.

The course of the reaction between ammonia and an α-(α-bromoacylamido)-ketone (I) is controlled by the nature of the substituent R; if this is a hydrogen atom, reaction proceeds to give a 2-acylamidopyrazine (VI). When R is an alkyl or aryl group, the reaction leads to a hydroxypyrazine (II) and, where R is the carbethoxy-group, it gives a 1 : 4-oxazine derivative. The formation of a 1 : 4-oxazine derivative is dependent upon a high degree of enolisation induced in the carbonyl group of the compounds (VII) by the neighbouring carbethoxyl group, a view supported by the observation that 3-(α-bromopropionamido)butan-2-one, which on treatment with ammonia gives 3-hydroxy-2 : 5 : 6-trimethylpyrazine (Newbold and Spring, *loc. cit.*), on reaction with sodium ethoxide gives 3-(α-ethoxypropionamido)butan-2-one and not 5-hydroxy-2 : 3 : 6-trimethyl-1 : 4-oxazine. Similarly, treatment of either α-bromopropionamidoacetone or ω-(α-bromopropionamido)acetophenone with sodium ethoxide in each case leads to simple replacement of halogen by an ethoxy-group to give α-ethoxypropionamidoacetone and ω-(α-ethoxypropionamido)acetophenone, respectively. In each case the yield of ethoxy-derivative is high and in neither case is the formation of a 1 : 4-oxazine observed.

Experimental.

Ethyl α-(α-Bromopropionamido)-β-ketobutyrate.—A stirred suspension of ethyl α-amino-β-ketobutyrate hydrochloride (10·0 g.) in dry chloroform (150 c.c.), to which was added a solution of α-bromopropionyl chloride (11·0 g.) in dry chloroform (50 c.c.), was cooled to 0° and treated with *N*-methylmorpholine (13·0 g.) in dry chloroform (25 c.c.) added dropwise during 30 minutes; the reaction mixture was stirred for 1 hour at 0°, then washed successively with water, dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4), and the chloroform removed under reduced pressure. The residue, which solidified, was crystallised from light petroleum (b. p. 40—60°), from which *ethyl α-(α-bromopropionamido)-β-ketobutyrate* (13·0 g., 84%) separated as needles, m. p. 70° (Found: C, 38·5; H, 5·0; N, 5·0. $C_9H_{14}O_4NBr$ requires C, 38·6; H, 5·0; N, 5·0%).

Ethyl α-Bromoacetamido-β-ketobutyrate.—The method described above being used, ethyl α-amino-β-ketobutyrate hydrochloride (13·5 g.) was treated with bromoacetyl chloride (15·0 g.) in the presence of *N*-methylmorpholine (20·0 g.) to give *ethyl α-bromoacetamido-β-ketobutyrate* (16·5 g., 83%), which separated from light petroleum (b. p. 80—100°) as needles, m. p. 99° (Found: C, 36·2; H, 4·5; N, 5·1. $C_8H_{12}O_4NBr$ requires C, 36·1; H, 4·5; N, 5·3%). Both acylamidoketobutyrates are insoluble in water, readily soluble in the common organic solvents, and give a claret-red colour with aqueous ethanolic ferric chloride solution.

Ethyl 5-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate.—(*a*) A solution of ethyl α-(α-bromopropionamido)-β-ketobutyrate (10·0 g.) in liquid ammonia (100 c.c.) containing ammonium iodide (0·5 g.) was kept in an autoclave at 15° for 16 hours. After removal of the ammonia, the residue was extracted (Soxhlet) with light petroleum (b. p. 60—80°). Concentration of the extract gave *ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate* (4·3 g., 61%) as needles, m. p. 96° (Found: C, 54·1, 54·3; H, 6·5, 6·8; N, 7·3, 6·8. $C_9H_{13}O_4N$ requires C, 54·3; H, 6·5; N, 7·0%). Light absorption (ethanol): Maxima at 2300 A. (ε = 7100) and 2800 A. (ε = 5600).

(*b*) A solution of ethyl α-(α-bromopropionamido)-β-ketobutyrate (0·80 g.) in ethanol (2 c.c.) was added to a solution of sodium ethoxide, from sodium (0·07 g.) and ethanol (2 c.c.). After being kept overnight at 15° the solvent was removed under reduced pressure, and the residue extracted with boiling light petroleum (b. p. 60—80°; 3 × 10 c.c.). Ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate (0·4 g.) separated on cooling as needles, m. p. 96° alone or mixed with the specimen described under (*a*).

Ethyl 5-Hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate.—(*a*) Ethyl α-bromoacetamido-β-ketobutyrate (5·1 g.) was treated with liquid ammonia as described above. Removal of the ammonia gave a gummy residue which was extracted with light petroleum (b. p. 80—100°; 6 × 25 c.c.); concentration of the extract under reduced pressure gave *ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate* (0·5 g., 14%) as needles, m. p. 112° (Found: C, 51·6; H, 5·9; N, 7·85. $C_8H_{11}O_4N$ requires C, 51·9; H, 5·9; N, 7·6%). Light absorption (ethanol): Maxima at 2300 A. (ε = 6800) and 2800 A. (ε = 5400).

(*b*) Ethyl α-bromoacetamido-β-ketobutyrate (4·1 g.) in dry ethanol (25 c.c.) was treated with a solution of sodium ethoxide, from sodium (0·4 g.) and ethanol (5 c.c.), at 15° and kept at this temperature for 16 hours. Evaporation of the ethanol under reduced pressure and extraction (Soxhlet) of the residue with light petroleum (b. p. 60—80°) gave ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate (1·55 g., 54·5%) as needles, m. p. 112° either alone or when mixed with the specimen prepared by method (*a*).

5-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylic Acid.—A suspension of ethyl 5-hydroxy-2 : 6-dimethyloxazine-3-carboxylate (3·0 g.) in aqueous sodium hydroxide (150 c.c.; 0·1N.) was shaken at 15°. After 16 hours, when dissolution was complete, the mixture was acidified to pH 4·0 with hydrochloric acid and evaporated under reduced pressure to half-bulk. After cooling to 5° the crystalline solid was separated, washed with ethanol, and dried in air (2·15 g., 83%). *5-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylic acid* separates from methanol as prisms, m. p. 214° (decomp.) (Found: C, 49·6; H, 5·6; N,

8·3%; equiv., 172. $C_7H_9O_4N$ requires C, 49·1; H, 5·3; N, 8·2%; equiv., 171). Light absorption (ethanol): Maxima at 2300 A. (ε = 7100) and 2800 A. (ε = 5900).

5-Hydroxy-2-methyl-1 : 4-oxazine-3-carboxylic acid was similarly obtained from its ethyl ester in 61% yield. It crystallised from methanol as prisms, m. p. 226° (decomp.) (Found: C, 46·1; H, 4·3; N, 9·4%; equiv., 161. $C_6H_7O_4N$ requires C, 45·9; H, 4·5; N, 8·9%; equiv., 157). Light absorption (ethanol): Maxima at 2260 A. (ε = 6900) and 2800 A. (ε = 5800).

3-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine.—3-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylic acid (200 mg.) was heated to 235° at atmospheric pressure for 15 minutes, effervescence then having ceased. Sublimation of the residue at 120°/1 mm. gave *3-hydroxy-2 : 6-dimethyl-1 : 4-oxazine* as plates, m. p. 73° (40 mg.) (Found: C, 56·8; H, 7·15; N, 10·9. $C_6H_9O_2N$ requires C, 56·7; H, 7·1; N, 11·0%). Light absorption (ethanol): Maximum at 2680 A. (ε = 3800). The compound, which is extremely hygroscopic, is soluble in the cold in the common solvents with the exception of light petroleum.

5-Hydroxy-2-methyl-1 : 4-oxazine.—5-Hydroxy-2-methyl-1 : 4-oxazine-3-carboxylic acid (100 mg.) was kept at 250° for 15 minutes at atmospheric pressure. The product was distilled at 120°/3 mm. to give a colourless oil, which solidified. Sublimation at 80°/0·5 mm. gave *5-hydroxy-2-methyl-1 : 4-oxazine* (20 mg.) as hygroscopic prisms, m. p. 54—55° (Found: C, 52·95; H, 6·4; N, 12·3. $C_5H_7O_2N$ requires C, 53·2; H, 6·2; N, 12·4%). Light absorption (ethanol): Maximum at 2680 A. (ε = 4300).

3-(α-Ethoxypropionamido)butan-2-one.—A solution of 3-(α-bromopropionamido)butan-2-one (1·5 g.) in dry ethanol (15 c.c.) was added to a cold solution of sodium ethoxide, from sodium (0·2 g.) and ethanol (5 c.c.), and kept at 15° for 36 hours. The red solution was separated from sodium bromide and evaporated to dryness under reduced pressure, and the residue extracted with boiling light petroleum (b. p. 80—100°; 3 × 5 c.c.). Removal of the solvent from the extract gave an oil which solidified on cooling. Sublimation at 70°/0·1 mm. followed by crystallisation from light petroleum (b. p. 60—80°) gave *3-(α-ethoxypropionamido)butan-2-one* (0·66 g.) as prisms, m. p. 45° (Found: C, 57·3; H, 9·0; N, 7·4. $C_9H_{17}O_3N$ requires C, 57·7; H, 9·1; N, 7·5%).

α-Ethoxypropionamidoacetone.—α-Bromopropionamidoacetone (0·8 g.) in dry ethanol (10 c.c.) was added to a solution of sodium ethoxide, from sodium (0·11 g.) and ethanol (5 c.c.), and the solution left overnight at 15°. The reaction mixture, filtered from sodium bromide, was evaporated under reduced pressure to give a gum. Sublimation at 60°/0·5 mm. gave *α-ethoxypropionamidoacetone* (0·2 g.) as hygroscopic needles, m. p. 65° (Found: C, 55·4; H, 8·7; N, 8·3. $C_8H_{15}O_3N$ requires C, 55·5; H, 8·7; N, 8·1%).

ω-(α-Ethoxypropionamido)acetophenone.—ω-(α-Bromopropionamido)acetophenone (2·5 g.) in dry ethanol (15 c.c.) was treated with a solution of sodium ethoxide, from sodium (0·3 g.) and ethanol (5 c.c.). After 36 hours at 15° the ethanol was removed under reduced pressure and the residue extracted with boiling light petroleum (b. p. 100—120°; 10 × 10 c.c.). Concentration of the extract gave *ω-(α-ethoxypropionamido)acetophenone* (270 mg.) as needles, m. p. 89° (Found: C, 66·5; H, 7·4; N, 6·3. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·2; N, 6·0%).

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185. *Stereochemistry of Metabolic Diols from Naphthalene and Anthracene.*

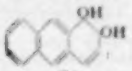
By J. W. COOK, J. D. LOUDON, and W. F. WILLIAMSON.

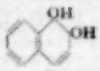
Resolution of *trans*-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-diol, through the *diesters* of *lævo*-menthoxyacetic acid, affords the *dextro-trans-* and *lævo-trans*-diols. The former of these is identical with the product obtained by hydrogenating the *lævo*-1 : 2-dihydronaphthalene-1 : 2-diol which was isolated by Young (*Biochem. J.*, 1947, **41**, 417) from the urine of rats dosed with naphthalene and which, accordingly, has the *trans*-structure.

(±)-*cis*- and (±)-*trans*-1 : 2 : 3 : 4-Tetrahydroanthracene-1 : 2-diols have been synthesised and characterised. The properties of the (±)-*trans*-diol correspond with those described by Boyland and Levi (*ibid.*, 1935, **29**, 2679; cf. Booth and Boyland, *ibid.*, 1949, **44**, 361) for the hydrogenation product of the (±)-metabolite which is formed when anthracene is fed to rats or rabbits.

BOYLAND and LEVI (*Biochem. J.*, 1935, **29**, 2679) showed that anthracene, fed to rats and rabbits, is converted in part into lævorotatory and inactive forms, respectively, of the diol (I). Young (*loc. cit.*) isolated a lævorotatory form of the diol (II) from the urine of rats dosed with naphthalene. According to Booth and Boyland (*ibid.*, 1949, **44**, 361), the respective diols (I) and (II) are obtained in each case as a mixture of an optically active and an inactive form, the dextrorotatory predominating in the metabolites from rabbits, the lævorotatory in those from rats. Theoretically the diols can exist in *cis-* and *trans*-modifications and to each modification there will be *dextro-*, *lævo-*, and inactive forms. It is of interest in relation to the mechanism of biological oxidation to determine the stereochemical form(s) of these metabolites, and when the present investigation was begun the only guide was provided by the work of Boyland and

Shoppee (*J.*, 1947, 801), who inferred a *cis*-configuration for the metabolites (I) from the rapidity with which these diols were oxidised by lead tetra-acetate. Recently, however, in view of the negative response to Criegee's reagent for *cis*-diols (*viz.*, triacetylosmic acid, cf. Criegee, Marchand, and Wannowius, *Annalen*, 1942, **550**, 99), Booth and Boyland (*loc. cit.*) have preferred the *trans*-configuration for the anthracene metabolites and have supported the same configuration for the naphthalene metabolites by extensive evidence which in part anticipates our own.


(I.)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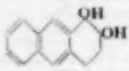
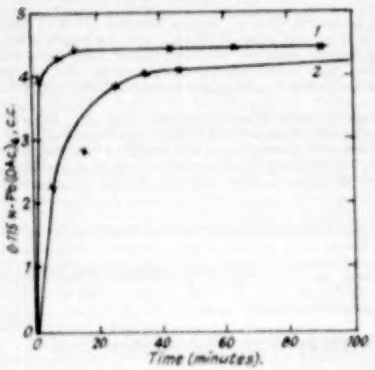

(III.)

(IV.)

The metabolites (I) and (II) are readily hydrogenated to the tetrahydro-diols (III) and (IV) respectively (Boyland and Levi, *loc. cit.*; Young, *loc. cit.*), and it was the aim of the present investigation to secure for reference and for optical resolution the *cis*- and *trans*-forms of these (±)-tetrahydro-diols. Straus and Rohrbacher (*Ber.*, 1921, **54**, 40) obtained the (±)-diol (IV) in *cis*- and *trans*-forms respectively by oxidation of 1 : 2-dihydronaphthalene with potassium permanganate and by stepwise hydrolysis of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydronaphthalene. These are satisfactory methods of preparation, and confirmation of the configurations assigned follows from (*a*) the results of applying to 1 : 2-dihydronaphthalene well-authenticated modern methods for *cis*- or *trans*-hydroxylation of a double bond (cf. Experimental), (*b*) tests with potassium triacetylosmate (cf. Experimental), and (*c*) the relative rates of oxidation by lead tetra-acetate determined by Criegee, Kraft, and Rank (*Annalen*, 1933, **507**, 159).

Oxidation of 1/4000 *mol. of* (1) *cis- and* (2) *trans-*1 : 2*-dihydroxy-*1 : 2 : 3 : 4*-tetrahydroanthracene with lead tetra-acetate.*



Resolution of *trans*-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-diol was effected through *diesters* produced by acylation with *lævo*-menthoxyacetyl chloride (cf. Wilson and Read, *J.*, 1935, 1269). The esters were separated by fractional crystallisation from light petroleum and on hydrolysis afforded the dextro-trans- and lævo-trans-*diols* (IV). The former diol was found to be identical in m. p. and specific rotation with a dextrorotatory specimen of the hydrogenated metabolite, which was kindly supplied by Professor L. Young: the m. p.s of the diacetates were also identical and were unaffected by admixture of the two samples. Attempts to resolve the *cis*-diol (IV) by the same means or through esters of *lævo*-menthylglycine (cf. Clark and Read, *J.*, 1934, 1775) were unsuccessful because of failure to obtain the esters in crystalline form.

For the synthesis of the *cis*- and *trans*-1 : 2 : 3 : 4-tetrahydroanthracene-1 : 2-diols (III), 2-anthrol was hydrogenated under pressure in the presence of copper chromite to an easily separable mixture of 9 : 10-dihydro- and 1 : 2 : 3 : 4-tetrahydro-2-anthrol. Von Braun and Bayer (*Annalen*, 1929, **472**, 105) reported the dehydration of the latter compound by distillation of the phenylurethane, but a more satisfactory method consists in heating the tetrahydroanthrol with fused potassium hydroxide. 1 : 2-Dihydroanthracene, so obtained, was converted, by treatment with osmium tetroxide in benzene–pyridine and subsequent hydrolysis of the ester complex, into the *cis*-diol (III), and the corresponding *trans*-diol was prepared (*a*) by hydrolysis of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydroanthracene *via* 1(or 2)-*bromo*-2(or 1)-*hydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene*, (*b*) together with some *cis*-diol, by oxidation of 1 : 2-dihydroanthracene with lead tetra-acetate.

The configuration assigned to these two diols is implicit in their respective methods of preparation and is confirmed by the fact that the isomer designated *cis*, alone of the pair, induces a colour change in the test with potassium triacetylosmate. Further confirmation is afforded

by the relative rates of oxidation by lead tetra-acetate (see Fig.), the *cis*-isomer showing the expected higher rate. It will be observed that in each case oxidation of the diol corresponds to the consumption of one molar proportion of lead tetra-acetate, and in this respect there is correspondence with the data recorded by Boyland and Shoppee (*loc. cit.*) for oxidation of the *laevo*- and inactive metabolites (I). These authors are consequently in error in interpreting their results as showing the consumption of two moles of lead tetra-acetate with concurrent (or consecutive) oxidation of the diol grouping and of the *meso*-positions in (I). It is in any case clear that analogy between the *meso*-positions in anthracene and the corresponding positions in (I) is unsound.

Attempts to resolve the *cis*- and *trans*-diols (III) were unsuccessful, but the m. p.s of the synthesised (±)-*trans*-isomer and of the derived diacetate closely correspond with those reported by Boyland and Levi (*loc. cit.*) for the hydrogenated (±)-metabolite and its diacetate.

Experimental.

(±)-cis-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (IV).—(i) 1 : 2-Dihydronaphthalene (1 g.) (Bamberger and Lodter, *Ber.*, 1890, **23**, 208) was added to a solution of osmium tetroxide (2 g.) in dry ether (40 c.c.). After 7 days the solution was evaporated to dryness and the residue was refluxed for 3 hours with a solution of sodium sulphite heptahydrate (8 g.) in water (40 c.c.) and ethanol (20 c.c.). After filtration (hot) and removal of most of the alcohol, (±)-*cis*-1 : 2-dihydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene (IV) was recovered in chloroform; it had m. p. 101° (from benzene) (Straus and Rohrbacher, *loc. cit.*, give m. p. 100—101°).

(ii) To 3·25 c.c. of a dried solution of hydrogen peroxide (5 c.c.; 90% by weight) in *tert.*-butyl alcohol (50 c.c.) were added, at 0°, 1 : 2-dihydronaphthalene (1 g.) and a solution of osmium tetroxide (0·1 g.) in *tert.*-butyl alcohol (10 c.c.). After 8 days at 0° the solution was concentrated under reduced pressure and the tarry residue was extracted with boiling water. The brown oil obtained by concentration of the aqueous extracts afforded, on recovery from benzene, the (±)-*cis*-diol (IV), m. p. 90—100°.

(±)-trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—To a dried solution of hydrogen peroxide (0·5 g.) in *tert.*-butyl alcohol (2 c.c.) were added at 0° 1 : 2-dihydronaphthalene (2 g.) and a solution of selenium dioxide (0·06 g.) in *tert.*-butyl alcohol. After 8 days at 0° concentration afforded (±)-*trans*-diol (IV), m. p. 112° (from benzene) (Straus and Rohrbacher, *loc. cit.*, give m. p. 112—113°).

Criegee, Marchand, and Wannowius (*loc. cit.*, 1942) reported *trans*-1 : 2-dihydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene (IV) to be exceptional (like *trans-cyclo*hexane-1 : 2-diol) in forming a diester with potassium triacetyloosmate. Booth and Boyland (*loc. cit.*), without comment on this point, state that the reagent provides the usual distinction between these *cis*- and *trans*-diols. Re-examination showed that there is a marked difference in behaviour between the two forms: the *cis*-form gave immediately a rapid change from blue through green and red to brown, whereas with the *trans*-form no immediate change was perceptible, but after 30 minutes the blue had been replaced by a purple colour.

Resolution of (±)-trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—Attempts were first directed to the formation of a monoester (cf. Wilson and Read, *J.*, 1935, 1269) by the addition of freshly distilled (−)-menthoxyacetyl chloride (23·4 g., 1·4 mols.) (*Org. Synth.*, **23**, 52) to a cooled solution of the (±)-*trans*-diol (IV) (12·6 g., 1 mol.) in pyridine (100 c.c.). After 16 hours at room temperature the solution was poured into water, and an ethereal extract, thoroughly washed in turn with dilute hydrochloric acid, dilute sodium hydroxide, and water, and dried (Na_2SO_4), afforded a viscous oil which partly solidified when rubbed with light petroleum (b. p. 60—80°). This solid (24·5 g.), however, was found to contain unchanged diol and accordingly was treated as above with a further quantity of (−)-menthoxyacetyl chloride (29·9 g.; 1·8 mols.). The resulting solid (33 g.) was separated by fractional crystallisation from light petroleum (b. p. 60—80°) into a less soluble *diester* (A), m. p. 116—117°, $[\alpha]_D^{15}$ −21° (*c*, 1·0 in chloroform) (Found: C, 73·6; H, 9·2. $C_{34}H_{44}O_8$ requires C, 73·4; H, 9·3%), and a more soluble *diester* (B), m. p. 101—102°, $[\alpha]_D^{15}$ −170° (*c*, 1·0 in chloroform) (Found: C, 73·4; H, 9·3%). The nature of these compounds as diesters (not conclusively shown by analysis—calc. for $C_{32}H_{44}O_8$: C, 73·3; H, 8·9%) was supported by the observed consumption of 8·41 c.c. of 0·4095*N*-methanolic potassium hydroxide (≏ 2 moles) in hydrolysis of 0·0679 g. of ester (A). The diester (A) (8 g.) was heated under reflux for 3 hours with 2·5% methanolic potassium hydroxide (90 c.c.). Removal of the alcohol and recovery with ether afforded (−)-trans-1 : 2-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*, m. p. 114—115° (from benzene), $[\alpha]_D^{15}$ −134° (*c*, 1·0 in chloroform) (Found: C, 73·4; H, 7·4. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%). When a solution of the diol (213 mg.) in pyridine (4 c.c.) was treated at 0° with acetic anhydride (1 c.c.) and, after 12 hours, poured into ice and dilute sulphuric acid, the corresponding *diacetate*, m. p. 66—67° (from light petroleum (b. p. >120°)), was obtained: $[\alpha]_D^{15}$ +126° (*c*, 1·0 in chloroform) (Found: C, 67·8; H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·4%). Similar treatment of the diester (B) afforded (+)-trans-1 : 2-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*, m. p. 114—115° (from benzene), $[\alpha]_D^{15}$ +132° (*c*, 1·0 in chloroform), $[\alpha]_D^{15}$ +64° (*c*, 0·5 in ethanol), $[\alpha]_{5461}^{15}$ +44° (*c*, 0·5 in ethanol) (Found: C, 73·2; H, 7·1. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%), and its *diacetate*, m. p. 66—67° (from light petroleum (b. p. >120°)), $[\alpha]_D^{15}$ −125° (*c*, 1·0 in chloroform) (Found: C, 67·7; H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·4%).

Young (*loc. cit.*) records for the (+)-hydrogenated metabolite (II) m. p. 115°, $[\alpha]_D^{22}$ +62° (*c*, 0·5 in ethanol), and a specimen kindly supplied by Professor Young did not depress the m. p. of (+)-*trans*-1 : 2-dihydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene and afforded a diacetate identical in micro-m. p. and mixed micro-m. p. with (−)-*trans*-1 : 2-diacetoxy-1 : 2 : 3 : 4-tetrahydronaphthalene.

1 : 2 : 3 : 4-*Tetrahydro*-2-*anthrol*.—2-Anthrol (10 g.) (Lagodzinski, *Annalen*, 1905, **342**, 68) in ethanol (100 c.c.) was hydrogenated in the presence of copper chromite (1 g.) at 200°/122 atm. for 7 hours. The crystalline solid, recovered from the filtered solution, was dissolved in ether and freed from 9 : 10-dihydro-

2-anthrol (m. p. 129°; *cf.* von Braun and Bayer, *loc. cit.*) by shaking the solution with 20% sodium hydroxide. 1 : 2 : 3 : 4-Tetrahydro-2-anthrol, recovered from the washed ethereal solution, had m. p. 142° (from ethanol) (Found : C, 85·1; H, 6·8. Calc. for $C_{14}H_{14}O$: C, 84·9; H, 7·1%) (von Braun and Bayer, *loc. cit.*, give m. p. 148°).

1 : 2-*Dihydroanthracene*.—1 : 2 : 3 : 4-Tetrahydro-2-anthrol (4 g.) was heated for 1 hour with freshly fused potassium hydroxide (4 g.) at 180—210°. The product, recovered from ether, was sublimed at 100—120°/3 mm., and had m. p. 147—148° (from ethanol) (von Braun and Bayer, *loc. cit.*, record m. p. 150°) (Found : C, 93·4; H, 6·7. Calc. for $C_{14}H_{12}$: C, 93·3; H, 6·7%).

(±)-cis-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene* (III).—A solution of 1 : 2-dihydroanthracene (1·42 g.) in dry ether (10 c.c.) was added to a solution of osmium tetroxide (2 g.) in ether (100 c.c.) and pyridine (1·4 c.c.). After 16 hours the precipitate was collected and heated under reflux for 1 hour with a solution of sodium sulphite heptahydrate (8·1 g.) in water (40 c.c.) and ethanol (20 c.c.). After filtration (hot) and removal of most of the ethanol, the *diol* crystallised and had m. p. 133—135° (from benzene) (Found : C, 78·7; H, 6·6. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). When a solution of the diol (125 mg.) in pyridine (2 c.c.) was treated at 0° with acetic anhydride (0·5 c.c.) and, after 12 hours at room temperature, was poured into iced water, the corresponding *diacetate*, m. p. 122° [from light petroleum (b. p. 60—80°)], was obtained (Found : C, 72·1; H, 6·2. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%).

(±)-trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene* (III).—(i) To a solution of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydroanthracene (2 g.) [m. p. 105—106° (from light petroleum, b. p. 60—80°); von Braun and Bayer, *loc. cit.*, record m. p. 102°] in acetone–water (4 : 1), kept at 50—60°, magnesium carbonate (1 g.) was added during 2·5 hours. The brown oil, obtained after filtration (hot) and removal of acetone, was extracted and dried in ether affording, on concentration, 1(or 2)-*bromo*-2(or 1)-*hydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene*, m. p. 102—103° [from light petroleum (b. p. 60—80°)] (Found : C, 60·6; H, 4·8. $C_{14}H_{13}OBr$ requires C, 60·6; H, 4·7%). This compound (0·5 g.) was heated under reflux for 1 hour with potassium hydroxide (0·15 g.) in water (10 c.c.). The *diol* recovered from ether had m. p. 162—163° (from benzene) (Found : C, 78·4; H, 6·8. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

(ii) 1 : 2-Dihydroanthracene (10 g.) was added to a solution of lead tetra-acetate (24 g.) in acetic acid (400 c.c.) and the mixture was heated at 80—90° for 1 hour. The cooled solution was poured into water, from which extraction with ether and recovery from the washed and dried ethereal extract gave an oil. This was hydrolysed by being heated under reflux (15 minutes) with potassium hydroxide (33 g.) in ethanol (500 c.c.). Subsequent dilution with water, removal of most of the ethanol, and recovery in ether afforded a mixture of *cis*- and *trans*-diols (III), which was separated by fractional crystallisation from benzene, the *trans*-form being the less soluble.

When a solution of the *trans*-diol (III) (118 mg.) in pyridine (2 c.c.) was treated with acetic anhydride (0·6 c.c.) and, after 12 hours at room temperature, was poured into iced water, the corresponding *diacetate*, m. p. 85—87° [from light petroleum (b. p. 60—80°)], was obtained (Found : C, 72·5; H, 6·2. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%). Hydrolysis of this diacetate regenerated the *trans*-diol, m. p. 162° [Boyland and Levi, *loc. cit.*, record m. p. 162° for the (±)-hydrogenated metabolite (II) and m. p. 84° for its diacetate].

Rate of Oxidation of cis- *and* trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene with Lead Tetra-acetate*.—To a solution of the diol (53 mg.) in acetic acid (10 c.c. distilled over chromium trioxide) kept at 18—19° by immersion in a thermostat, were rapidly added 10 c.c. of a standard solution of lead tetra-acetate, the time of addition being noted. At intervals, samples (1 c.c.) were withdrawn and run into a potassium iodide–sodium acetate buffer solution, and the liberated iodine was titrated against standard sodium thiosulphate. The results are given in the figure.

The *cis*-diol (III) produced an immediate change from blue to green; the *trans*-diol caused no change in the colour of potassium triacetyliosmate.

We are indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance (to W. F. W.) and to Professor Leslie Young for a sample of his reduced metabolite from naphthalene. Micro-analyses were carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

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186. *An Infra-red Spectroscopic Investigation of Double-bond Structure in Simple Acyclic Terpenes and Derivatives thereof.*

By D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard, and G. B. B. M. Sutherland.

The infra-red spectra of twenty-five purified acyclic monoterpene compounds are described and discussed with particular reference to the position and configuration of the double bonds. A semi-quantitative method for the infra-red detection of *iso*propenyl end-groups is outlined, and the present experimental results as well as those recorded by Thompson and Whiffen are interpreted on this basis. Very strong evidence is obtained that naturally occurring acyclic monoterpenes as a class possess the homogeneous *iso*propylidene end-group structure. In every purified sample examined by us, the proportion of the compound in the *iso*propenyl form never exceeded 3%, and was usually very much less or possibly nil. Classical oxidative degradations afford indecisive conclusions in this field.

Some of the characteristic vibration frequencies of alcohol, ether, and vinyl groupings are shown to be modified if they occur in an allylic environment.

The nature of " geranyl chloride " as an anionotropic mixture of primary with some tertiary halide has been established by infra-red analysis of the partly resolved fractions resulting from low-pressure distillation.

A simple unresolved structural problem in organic chemistry is the question of the position of the double bond in the terminal *iso*propylidene (I) or *iso*propenyl (II) groups of acyclic monoterpenes and related substances (cf. Simonsen and Owen, " The Terpenes," Cambridge, 1947; *Endeavour*, 1949, **8**, 26). On oxidative degradation, such compounds generally behave as if they were mixtures of (I) with a smaller and variable proportion of (II), but there is other evidence suggesting that the terpenes are structurally homogeneous and that the ambiguous results of oxidation must be attributed to partial rearrangement. *E.g.*, Kuhn and Roth (*Ber.*, 1932, **65**, 1285) found that the ultra-violet absorption curves of the two crystalline *cis-trans*-isomeric dehydrogeranic acids (III) were incompatible with the presence of some 30%

$CMe_2{:}CHR$ (I.) $CH_2{:}CMe{\cdot}CH_2R$ (II.) $CMe_2{:}CH{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2H$ (III.)

$CH_2{:}CMe{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2H$ (IV.) $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CHX$ (V.) $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2X$ (VI.)

of the less highly conjugated *iso*propenyl form (IV) which is required by ozonolytic evidence (Cahn, Penfold, and Simonsen, *J.*, 1931, 3134; Kuhn and Roth, *loc. cit.*). Recent chemical work on the two crystalline *cis-trans*-isomeric geranamides (V; X = $CO{\cdot}NH_2$) (Caldwell and Jones, *J.*, 1946, 599), and the *X*-ray crystal-structure analysis of geranylamine hydrochloride (VI; X = NH_3Cl) (Jeffrey, *Proc. Roy. Soc.*, 1945, *A*, **183**, 388; cf. Sutton, *J.*, 1944, 306) also support the view that these crystalline acyclic terpene derivatives are homogeneous *iso*propylidene compounds, and that much of the older chemical work purporting to prove the presence of *iso*propenyl (II) as well as *iso*propylidene (I) end-groups is of doubtful value.

Quite generally, the use of oxidative degradation as an unequivocal method of detailed structure diagnosis has become increasingly suspect during recent years (see, *e.g.*, Clemo and Macdonald, *J.*, 1935, 1294; Karrer and Bretscher, *Helv. Chim. Acta*, 1943, **26**, 1758; Caldwell and Jones, *loc. cit.*; Young, McKinnis, Webb, and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 293). Accordingly, physical methods of structure analysis are desirable, and the present paper is the outcome of work initiated five years ago after a study of crystalline geranylamine hydrochloride. The methods and conclusions are set out in detail below. Very strong evidence has been obtained for the absence of *iso*propenyl end-groups (II) from the structure of simple acyclic terpenoid compounds. At the same time, useful information has become available about the allylic isomerism of the second double bond in molecules such as geranyl chloride and its derivatives.

Earlier Spectroscopic Work.—Unconjugated acyclic terpenes do not display characteristic high-intensity absorption in the range 2000—4000 A. (cf. Bateman and Koch, *J.*, 1944, 600). Little significance can therefore be attached to the work of Savard (*Bull. Soc. chim.*, 1929, [iv], **45**, 398) who examined citronellol, rhodinol, and geraniol in this spectral region where the low-intensity absorption is non-selective and excessively sensitive to traces of chromophoric impurities. On the other hand, Kuhn and Roth's interpretation of the high-intensity ultra-violet absorption curves of the fully conjugated dehydrogeranic acids (*loc. cit.*), based on measurements by Hausser and Smakula, appears to be sound. Ultra-violet spectroscopical analysis of the structure of terpenes is restricted to the few special cases where conjugation occurs, and even there the sensitivity of the method is relatively limited. The application of Raman

spectroscopy was discussed and adversely criticised by Angus (*Indian Acad. Sci.*, Raman Jubilee Vol., **1935**, 529); at that time instrumentation and physical accuracy were sometimes still imperfect, few if any pure standards were available, and the purity of the investigated terpene samples was not always rigorously controlled before and during irradiation, but the usefulness and reliability of Raman data have now been firmly established (cf. Fenske *et al.*, *Ind. Eng. Chem. Anal.*, **1947**, **19**, 700; *Analyt. Chem.*, **1949**, **21**, 12). At the same time, infra-red absorption probably offers advantages over the Raman method of vibrational spectroscopy in resolving the *iso*propenyl–*iso*propylidene controversy. As a result of an enquiry from Sir John Simonsen, Thompson and Whiffen (*J.*, **1948**, 1412) thus examined various samples of acyclic terpenes and concluded that "in general, the compounds examined appear to be mixtures of the two forms containing terminal *iso*propenyl and *iso*propylidene groups" and that "the proportions of the two forms vary in different cases, but it may be significant that in the majority the *iso*propylidene type is predominant." No physical constants or other preparative details of their compounds were given, and the purity of some of their samples was known to be questionable. Thompson and Whiffen's conclusions must therefore be regarded as preliminary and the authors themselves were aware of this limitation in concluding their paper with the remarks: "It is evident that this problem might repay a more detailed study using a larger number of compounds, particular attention being paid to the origin or method of preparation, and to freedom from oxidation or impurities." With the aid of approximate extinction coefficients, it will be shown that both their and our results are in fact incompatible with the conclusion that most of the compounds contained *appreciable* amounts (15—50%) of *iso*propenyl end-groups as required by the evidence of oxidative degradation.

Physical Basis of the Present Analytical Method.—It has been amply established in recent years that the infra-red absorption spectra of olefinic hydrocarbon compounds are sharply differentiated according to the number and relative position (symmetrical or unsymmetrical, *cis* or *trans*) of one or more hydrogen atoms directly attached to the unsaturated carbon atoms (Thompson and Torkington, *Trans. Faraday Soc.*, **1945**, **41**, 246; Rasmussen and Brattain, *J. Chem. Physics*, **1947**, **15**, 120, 131, 135; Kilpatrick and Pitzer, *J. Res. Nat. Bur. Stand.*, **1947**, **38**, 191; Sheppard and Sutherland, *J.*, **1947**, 1540; *Proc. Roy. Soc.*, **1949**, *A*, **196**, 195; Amer. Petroleum Inst., "Catalog of Infra-Red Spectrograms," **1949**). The following *strong* bands due to out-of-plane deformational modes of vibration of the olefinic hydrogen atoms always occur at or near the frequencies indicated, whenever the requisite structural groupings are present (R = alkyl or substituted alkyl):

CHR:CR′R″	800—840 cm.$^{-1}$	CH_2:CRR′	890 cm.$^{-1}$
cis-CHR:CHR′	690 ,,	CH_2:CHR	910 and 990 cm.$^{-1}$
trans-CHR:CHR′	965 ,,		

No exception to these correlation rules has yet been found, although the A.P.I. catalogue alone lists some eighty unsaturated hydrocarbons. Failure to absorb at any of the given characteristic frequencies is therefore proof that the corresponding grouping is absent; in particular, the presence of *iso*propenyl groups may be safely discounted when no absorption occurs close to 890 cm.$^{-1}$ (at suitable path length). On the other hand, the appearance of bands at or near the given frequency positions does not necessarily indicate the presence of any of the above types of double bond, since other vibrations of the molecular framework often happen to give rise to absorption in this spectral region. For example, *n*-octane, 3-ethylhexane, 3-methyl-3-ethylpentane (A.P.I., *op. cit.*), and crystalline geranylamine hydrochloride (see below) display a marked absorption near 890 cm.$^{-1}$, although the CH_2:CRR′ grouping is certainly absent in these compounds. In many cases, the suspected presence of a given type of olefinic structure can be confirmed by reference to the C=C stretching frequency near 1660 cm.$^{-1}$ (Sheppard and Sutherland, *loc. cit.*, 1947; Thompson and Whiffen, *loc. cit.*); CHR:CR′R″ gives rise to an infra-red band near 1670 cm.$^{-1}$, but CH_2:CRR′ and CH_2:CHR absorb around 1645 cm.$^{-1}$. Here again, however, some caution must be exercised in the assignment of weak bands which may occasionally represent overtones or combinations of lower frequencies; both *cis*- and *trans*-3-methylpent-2-ene, for instance, exhibit absorption between 1620 and 1660 cm.$^{-1}$, although they do not contain a terminal methylene group (A.P.I., *op. cit.*). The position may be summarised by stating that *the* absence *of a particular double-bond structure in a hydrocarbon residue can be inferred with complete confidence from the absence of the characteristic infra-red frequencies at suitable path length, whereas additional evidence is sometimes required to prove the* presence *of a suspected grouping.*

In order to estimate the composition of isomeric mixtures and to fix an upper analytical limit

of detection for the infra-red method, we must know the molecular extinction coefficients of the characteristic olefinic bands. It has been pointed out elsewhere (Sheppard and Sutherland, *loc. cit.*, 1947) that both the characteristic hydrogen deformation and the double-bond stretching frequencies of $CH_2{:}CRR'$ (*e.g.*, *iso*propenyl) groupings exhibit relatively much greater absorption intensities than do the corresponding frequencies of $CHR{:}CR'R''$ (*e.g.*, *iso*propylidene) groups in the pure compounds. The sensitivity of the infra-red method of detecting the very strongly absorbing *iso*propenyl groups can be estimated from the approximate molar decadic extinction coefficients of a representative number of pure compounds which have now been determined in dilute solution and are listed in the table below.

Approximate infra-red extinction coefficients of isopropenyl and isopropylidene groups.

Compound.	Type.	Frequency (cm.$^{-1}$).	ε (litres.g.-mol.$^{-1}$ cm.$^{-1}$).
Geraniolene (mainly V; X = H)	*iso*Propenyl	890	120 (in CCl_4)
α-Lupene [1]	,,	885	150 ,,
Lupeol [2]	,,	883	200 (in CS_2)
2-Methylpent-1-en-4-one	,,	895 [3]	160 [3] ,,
2 : 3 : 3-Trimethylbut-1-ene	,,	890	155 (in CCl_4)
2 : 4 : 4-Trimethylpent-1-ene	,,	890	155 ,,
2-Methylpent-1-en-4-one	,,	1650 [3]	24 [3] ,,
2 : 3 : 3-Trimethylbut-1-ene	,,	1640	20 (in C_6H_{12})
2-Methylpent-2-ene	*iso*Propylidene	830	38 (in CS_2)
2-Methylbut-2-ene	,,	1680	$1 < \varepsilon < 10$ [4] (neat)

[1] A pentacyclic triterpene hydrocarbon, $C_{30}H_{50}$, of known structure (see Experimental). [2] A pentacyclic triterpene alcohol, $C_{30}H_{50}O$, of known structure (see Experimental). [3] Taken from A.P.I. spectrogram (*loc. cit.*, serial no. 634). [4] Estimated from one single spectral run. According to Kletz and Sumner (*J.*, 1948, 1456), the extinction coefficient of the *iso*propylidene C=C stretching frequency band in 2 : 4 : 4-trimethylpent-2-ene is about 0·35 times that of the corresponding *iso*propenyl absorption in 2 : 4 : 4-trimethylpent-1-ene.

Clearly, the extinction coefficient of the 890-cm.$^{-1}$ band of the *iso*propenyl group is much greater than that of either of the two characteristic *iso*propylidene bands or the 1645-cm.$^{-1}$ C=C stretching frequency of the *iso*propenyl double bond. The relatively low value of ε observed in geraniolene can almost certainly be ascribed to the presence of structural isomers in this hydrocarbon (cf. Simonsen and Owen, *op. cit.*; Naylor, *J.*, 1947, 1532), and the anomalously high value obtained for lupeol may not be reliable owing to the use of a different cell in this case (see Experimental). Whether or not the 890-cm.$^{-1}$ band extinction coefficient of the *iso*propenyl group remains *strictly* constant in different compounds (cf. Thompson and Whiffen, *loc. cit.*; Anderson and Seyfried, *Analyt. Chem.*, 1948, **20**, 998), it is evidently always high, and quite small amounts of *iso*propenyl groups could not escape detection by the infra-red method. As little as 1% of the hypothetical *iso*propenyl form of a simple terpene, for instance, would give rise to about 10% absorption in a 0·05-mm. path-length of the isomeric mixture.

According to the evidence of chemical oxidations provided by Grignard and his school, most acyclic monoterpenes contain 15—50% of the *iso*propenyl isomer admixed with an excess of the *iso*propylidene form (see Simonsen and Owen, *op. cit.*). On the basis of the above extinction coefficients, more than 70% absorption should then be displayed at the 890-cm.$^{-1}$ band when the spectrum is examined through a conventional path-length of 0·05 mm. of the liquid monoterpene. In actual fact, however, the absorption generally appears to be at most 10% of this, both in our own purified samples and in those examined by Thompson and Whiffen (particularly their citronellol " B," geranamide, citral, linalool, and dihydromyrcene " A "). Contrary to first impressions, therefore, Thompson and Whiffen's published data also indicate that the chemical evidence is in many instances altogether unreliable, and that many of the acyclic terpenes are almost, if not completely, homogeneous *iso*propylidene structures.

Experimental.

Most of the infra-red spectra were measured with one of two Hilger D 209 spectrometers: one at Cambridge was employed under double-beam conditions (cf. Sheppard and Sutherland, *loc. cit.*, 1947), and the other at Welwyn was employed as a single-beam instrument in an exhaustively dried atmosphere (humidity below 5%). Interference by water-vapour absorption in the 1640—1670-cm.$^{-1}$ region was therefore rendered insignificant. The spectra of a few samples, and most of the extinction coefficients given in the above table, were determined on a Grubb–Parsons single-beam instrument as described elsewhere (Barnard, Fabian, and Koch, *J.*, 1949, 2442). The effective slit widths employed were 3—5 cm.$^{-1}$ at 890 cm.$^{-1}$, and 7—10 cm.$^{-1}$ at 1650 cm.$^{-1}$. A fixed absorption cell (within a very small tolerance 0·1 mm. thick) was used for all extinction measurements, except in the case of lupeol which was investigated in a 0·25-mm. cell at higher molar dilution. The liquid terpene samples were studied as films from

0·05 to 0·1 mm. thick between sodium chloride plates, and the crystalline samples in suspension in "Nujol" as well as in solution as indicated. The commercial samples of the various terpenes were purchased from Messrs. Boake Roberts & Co., except when otherwise specified. All liquid compounds were freshly distilled and either examined immediately or kept sealed *in vacuo* between distillation and spectrographic examination.

Compounds used for Extinction-coefficient Measurements.—The sample of geraniolene (mainly V; X = H) was that described by Dr. R. F. Naylor elsewhere (*loc. cit.*). α-Lupene and lupeol were pure crystalline samples given to us by Professor E. R. H. Jones (cf. Heilbron, Kennedy, and Spring, *J.*, 1938, 329; Jones and Meakins, *J.*, 1941, 757). Pure 2 : 3 : 3-trimethylbut-1-ene was prepared by Dr. J. L. Holland by dehydration of 2 : 3 : 3-trimethylbutan-2-ol obtained from *tert.*-butylmagnesium chloride and acetone, and 2 : 4 : 4-trimethylpent-1-ene was a specially distilled sample obtained from Imperial Chemical Industries, Limited, through Dr. A. G. Evans. Dehydration of 2-methylpentan-2-ol with iodine afforded a mixture of 2-methylpent-2-ene with 2-methylpent-1-ene which gave the following fractions after distillation through a column packed with Dixon copper gauze (23 theoretical plates): (i) b. p. 64·3—66·0°/754 mm. (70 g.) (25% of 2-methylpent-1-ene); (ii) b. p. 66·0—66·4°/754 mm. (70 g.) (10% of 2-methylpent-1-ene); (iii) b. p. 66·5—66·6°/751 mm. (37 g.) (3% of 2-methylpent-1-ene); (iv) b. p. 66·6°/751 mm. (3·5 g.) (0·2% of 2-methylpent-1-ene). Fraction (iv) was used (the isomer contents in this preparation, which was made by Dr. J. I. Cunneen, were established by infra-red analysis). 2-Methylbut-2-ene was similarly prepared by Dr. A. W. Kenchington from 2-methylbutan-2-ol, and had n_D^{25} 1·3908 (2-methylbut-1-ene content, 0·1%).

2-Methylhept-2-en-6-one (VII). A commercial sample from Messrs. Boake Roberts & Co. afforded a solid semicarbazone only with considerable difficulty, even after fractionation (boiling range 59—70°/12 mm.; refractive index range n_D^{14} 1·4562—1·4430). A similar sample from Messrs. Hopkin and Williams Ltd. distilled over a much smaller range (55—57°/12 mm.; n_D^{14} 1·4625) and gave a good yield of solid semicarbazone from aqueous alcohol. The pure derivative was obtained in the form of colourless needles, m. p. 135·5—136° (bt., *ca.* 135°), after repeated crystallisation from benzene–light petroleum (b. p. 60—80°). Spectroscopically and otherwise identical ketone samples were obtained by regeneration from this semicarbazone by (*a*) steam-distillation with phthalic anhydride, or (*b*) prolonged cold treatment with 2*N*-sulphuric acid and light petroleum (b. p. 40—60°). Pure 2-methylhept-2-en-6-one has b. p. 58°/12 mm., n_D^{20} 1·4414 (we are indebted to Mr. A. L. Morris for these preparations). Another specimen was obtained directly by alkaline cleavage of citral (commercial grade), followed by simple fractionation (b. p. 66—66·5°/16 mm.; n_D^{20} 1·4420); it exhibited a spectrum indistinguishable from that of the products obtained as above from the pure semicarbazone.

(±)-*2-Methylhept-2-en-6-ol* (VIII). The above ketone was reduced with aluminium *iso*propoxide in *iso*propyl alcohol to give the corresponding alcohol as a colourless, slightly viscous liquid, b. p. 76·5—77°/14 mm., n_D^{15} 1·4515, n_D^{20} 1·4481.

Citronellol (3 : 7-*dimethyloct*-6-*en*-1-*ol*) (IX). Commercial citronellol ("C" and "Q" grades) is a complex mixture. On fractionation through a 15-plate column under reduced pressure, "C" grade was found to consist largely of material possessing almost exactly the b. p. (113·8—114·2°/14 mm.) and refractive index (n_D^{15} 1·4561) attributed to pure citronellol (Simonsen and Owen, *op. cit.*). "Q" Grade appears to be more heterogeneous. After neglecting a small fore-run, the following fractions were collected in approximately equal proportions: (i) b. p. 109—112°/17 mm., n_D^{15} 1·4498; (ii) b. p. 112—113·5°/17 mm., n_D^{15} 1·4535; (iii) b. p. 113·5—115°/17 mm., n_D^{15} 1·4598; (iv) a dark residue, n_D^{15} 1·4680.

Rhodinol (IX). The main bulk of a commercial sample had b. p. 117—118°/20 mm., n_D^{20} 1·4660.

Citronellal (3 : 7-*dimethyloct*-6-*en*-1-*al*) (X; X = O). Fractionation of the commercial product yielded a considerable amount of low-boiling material and a main fraction, b. p. 89·0—89·5/17 mm., n_D^{20} 1·4500.

Citronellal semicarbazone (X; X = N·NH·CO·NH_2). This was prepared from the above purified aldehyde according to the directions of Tiemann and Schmidt (*Ber.*, 1897, **30**, 34) and had m. p. 82·5° [after three crystallisations from light petroleum (b. p. 60—80°)].

Geraniol (3 : 7-*dimethylocta*-trans-2 : 6-*dien*-1-*ol*) (VI; X = OH). A commercial sample, purified *via* the calcium chloride adduct, had b. p. 114°/13 mm., n_D^{20} 1·4782. Another sample was specially prepared from the crystalline diphenylurethane (see below) which was decomposed in the usual manner, the last traces of admixed diphenylamine being removed chromatographically on alumina (geraniol was more strongly adsorbed). This specimen distilled at 110°/12 mm., and had n_D^{15} 1·4806 (free from diphenylamine according to the ultra-violet light absorption test). The two geraniol samples displayed identical infra-red spectra.

Nerol (3 : 7-*dimethylocta*-cis-2 : 6-*dien*-1-*ol*) (VI; X = OH). This alcohol was prepared in a pure state by extensive fractional crystallisation of the diphenylurethane mixture obtained from a commercial sample after 2 treatments with excess of calcium chloride. The final diphenylurethane (see below) was decomposed in the usual manner, and the regenerated alcohol freed from diphenylamine (ultra-violet light absorption test) by distillation and chromatography on alumina. This sample had b. p. 105°/12 mm., n_D^{15} 1·4795 (tetrabromide, silky needles, m. p. 116—118°). Another specimen (n_D^{15} 1·4749), kindly given us by Messrs. CIBA Ltd. of Basle, and said to contain a small proportion of geraniol, exhibited similar infra-red absorption.

Diphenylurethanes of geraniol and nerol (VI; X = O·OC·NPh$_2$). These well-known derivatives (cf. Simonsen and Owen, *op. cit.*) formed a continuous series of mixed crystals of space group C. 2/c. We are indebted to Dr. G. A. Jeffrey for the following crystallographic data:

Alcohol basis of derivative.	M. p.	Unit cell dimensions in A. [*a*].	[*b*].	[*c*].	β.	Vol. in A.^{3}.
Pure geraniol	80·5—81°	30·26	6·31	24·20	116·7°	4126
Mixture M	60—63	30·09	6·37	23·87	117·6	4055
Mixture N	52—55	30·01	6·44	23·67	118·4	4024
Pure nerol	50—51	29·96	6·50	23·55	119·0	4011

Geranamides **I** ***and*** **II** (trans- and cis-V; X = CO·NH_2). The preparation of these crystalline compounds is fully described elsewhere (Caldwell and Jones, *loc. cit.*; Barnard and Bateman, following paper).

Digeranyl (2 : 6 : 11 : 15-*tetramethylhexadeca*-2 : 6 : 10 : 14-*tetraene*) (XI) ***and*** *iso**digeranyl* (XV) These are described elsewhere (Barnard and Bateman, following paper).

Digeranyl ether (XII) (b. p. 153°/0·1 mm., n_D^{20} 1·4846). This was prepared by Dr. R. F. Naylor (*J.*, 1949, 2724) by interaction of geranyl chloride with the potassium derivative of geraniol in ethereal solution.

Homogeranic acid (VI; X = CO_2H) ***and*** *iso**homogeranic acid* (XIV; X = CO_2H). These and their respective amides are described elsewhere (Barnard and Bateman, following paper).

Geranylamine hydrochloride (1-*amino*-3 : 7-*dimethylocta*-trans-2 : 6-*diene hydrochloride*) (VI; X = NH_2Cl). This compound, m. p. 146°, has been fully described by Sutton (*loc. cit.*) and Jeffrey (*loc. cit.*).

Linalool (3 : 7-*dimethylocta*-1 : 6-*dien*-3-*ol*) (XIV; X = OH). Two commercial samples of different botanical origin (Bois de Rose and Bergamot) yielded on fractionation an identical main constituent, b. p. 86°/14 mm., n_D^{20} 1·4630.

Geranyl chloride (VI and XIV; X = Cl). This was prepared from geraniol as described elsewhere (following paper). A liquid boiling over the range 45—70°/0·2 mm. constituted 90% of the total yield. This was fractionated through a 30-cm. Vigreux column and separated into the following four equal fractions (Calc. for $C_{10}H_{17}Cl$: Cl, 20·56%): (i) b. p. 40—45°/0·2 mm., n_D^{20} 1·4710 (Found: Cl, 20·3%); (ii) b. p. 45—47·5°/0·2 mm., n_D^{20} 1·4738 (Found: Cl, 20·4%); (iii) b. p. 47·5—52°/0·2 mm., n_D^{20} 1·4777 (Found: Cl, 20·5%); (iv) b. p. 52—53°/0·2 mm., n_D^{20} 1·4797 (Found: Cl, 20·5%).

Results and Discussion.

The infra-red absorption curves of most of the compounds investigated are presented in the accompanying diagrams, and others are more briefly described in the course of the discussion. A summary of the observed group frequencies is also given in tabular form. In comparisons of

Group frequencies ($cm.^{-1}$).

(? signifies uncertain structural correlation; w, weak band; —, band absent. The usual CH_3 and CH_2 bands near 1450 and 1375 $cm.^{-1}$ are not shown.)

	Structure.	CH_2:CR_2.		CHR:CR_2.	CH_2:CHR.	CH_2.	C·O or C:O.
Methylheptenone	(VII)	—	—	810		735	1720
Methylheptenol	(VIII)	—		832, 1670	?908, ?990, ?1645 w	745	1120
Citronellol (rhodinol)	(IX)	?885 w,	?1645 w	830, 1670		738	1055
Citronellal	(X; X = O)	?900,	?1645	825, 1675		738	1720
Citronellal semicarbazone	(X; X = N·NH·CO·NH_2)	?900 w		840		740	
Geraniol	(VI; X = OH)	?888 w,	—	838, 1670		740	1010
Nerol	(VI; X = OH)	?888 w,	—	832, 1670		742	1010
Geranamides (CS_2 solution)	(V; X = CO·NH_2)	?900 w,		820, 825		745, 760	
Dimethyloctadiene	(VI; X = H)	?888 w,	—	820, 1678		740	
Dihydromyrcene	(VI; X = H and XIII)	889, —	1650	820, 1678		740	
Geraniolene	(V; X = H)	891,	1654	821, 1680		745	
Digeranyl	(XI)	?885 w,	—	832, 1670		738	
Digeranyl ether	(XII)	?887 w,	—	830, 1668		745	~1080
Homogeranic acid	(VI; X = CO_2H)	—		827		740	
Homogeranamide	(VI; X = CO·NH_2)	?888 w		825		742	
Geranylamine hydrochloride	(VI; X = NH_2Cl)	?888		835, 1670		725	
Geranyl chloride	(VI; X = Cl)	?890 w		845, 1665		745	
	(XIV; X = Cl)	?900 w		830	925, 990, 1415, 1645	745	
Linalool	(XIV; X = OH)	—		835, 1672	925, 997, 1415, 1645	740	1115
*iso*Digeranyl	XV	?885 w		832, 1670	908, 998, 1415, 1642	742	
*iso*Homogeranamide	(XIV; X = CO·NH_2)	—		835	920, 1005	730	

spectroscopic estimates for the maximum percentage of *iso*propenyl groups with deductions from chemical work, the latter values have been taken from the review by Simonsen and Owen (*op. cit.*).

CMe_2:$CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3$ (VII.)

CMe_2:$CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_3$ (VIII.)

CMe_2:$CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}OH$ (IX.)

CMe_2:$CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH$:X (X.)

Analysis of iso*Propenyl Groups.*—Methylheptenone (VII) and methylheptenol (VIII) are important degradation products of citral and geraniol respectively, and may be regarded as based on a common end-group structure of many simple acyclic terpenes. The infra-red spectra (Fig. 1) of both these simple compounds showed absence of absorption at 890 cm.$^{-1}$, so that no more than a fractional percentage of *iso*propenyl groups could have been present in the samples examined (see Introduction, p. 917).

Two commercial samples of the simplest terpene alcohol, citronellol (IX), were rather impure, but one of them ("C" grade) furnished on distillation a main fraction possessing physical constants identical with those given for the pure carbinol by Simonsen and Owen (*op. cit.*). This purified material, similarly to Thompson and Whiffen's citronellol "B," exhibited (Fig. 1) a weak band at 885 cm.$^{-1}$, accompanied by slight absorption near 1645 cm.$^{-1}$, so that a trivial amount (approximately 2% as estimated from the 885-cm.$^{-1}$ absorption) of the isomer containing the terminal *iso*propenyl double band *may* have been present. It will be shown below, however, that even this low proportion of terminal double bonds (if real) probably originated in some foreign impurity. Chemical evidence suggests that some 18—28% of the citronellol molecules exist in the *iso*propenyl form. A nearly identical spectrum was displayed by rhodinol (citronellol from a different source); a distinct enhancement of the characteristic *iso*propylidene double-bond absorption was almost certainly due to the presence of a small amount of the more highly unsaturated geraniol.

A commercial sample of citronellal (X; X = O) gave a spectrum very similar to that recorded by Thompson and Whiffen. This is compatible with the presence of some 5% of *iso*propenylic isomer or extraneous impurity; oxidative degradation indicates an isomer content of 40%. More significantly, the pure crystalline semicarbazone of this aldehyde (X; X = N·NH·CO·NH$_2$) displayed (Fig. 1) less than 5% absorption between 860 and 910 cm.$^{-1}$ in a path-length affording 30% absorption at the characteristic 840-cm.$^{-1}$ band of the *iso*propylidene group; an approximate calculation on the basis of these figures shows that the semicarbazone contains even less of the *iso*propenyl form than is allowed by the spectrum of purified citronellol (*i.e.*, less than 2%). Far from being an inseparable mixture of appreciable amounts of both *iso*propenyl and *iso*propylidene isomers as may be deduced on chemical grounds (see Simonsen and Owen, *op. cit.*), citronellal semicarbazone evidently exists in the homogeneous *iso*propylidene form (cf. Harries, *Annalen*, 1915, **410**, 1).

Differing from Thompson and Whiffen, we found that geraniol (VI; X = OH), purified in the usual manner *via* its solid adduct with calcium chloride, displayed (Fig. 1) no absorption peak near 1645 cm.$^{-1}$, and only a small band at 890 cm.$^{-1}$ (less than 1% of *iso*propenyl form present). The stereoisomeric nerol, regenerated from the diphenylurethane derivative, was similar in this respect (see Fig. 1). Oxidative data suggest the presence of over 20% of the *iso*propenyl isomers in these alcohols. Infra-red analysis of various chemical derivatives of geraniol, nerol, and the corresponding aldehydes, citral *a* and *b*, also supports the conclusion that the original alcohols are free from *iso*propenyl groups. Thus both the solid and the solution spectra of the two stereoisomeric geranamides (V; X = CO·NH$_2$) (see Fig. 2) are incompatible with the presence of more than 3% of this structural grouping. The dimethyloctadiene (VI; X = H), obtained by sodium–liquid ammonia reduction of geraniol, cannot contain as much as 2% of the *iso*propenyl isomer according to the spectrum already reported (Sheppard and Sutherland, *loc. cit.*, 1947; Thompson and Whiffen, *loc. cit.*), and the synthetic "double molecule" digeranyl (XI) has now been found to display closely similar absorption (Fig. 3). Again, the intensity of the band at 887 cm.$^{-1}$ in the spectrum of synthetic digeranyl ether (XII) (see Fig. 3), if attributed to *iso*propenyl structures, limits their proportion to 3% of the total end-groups present.

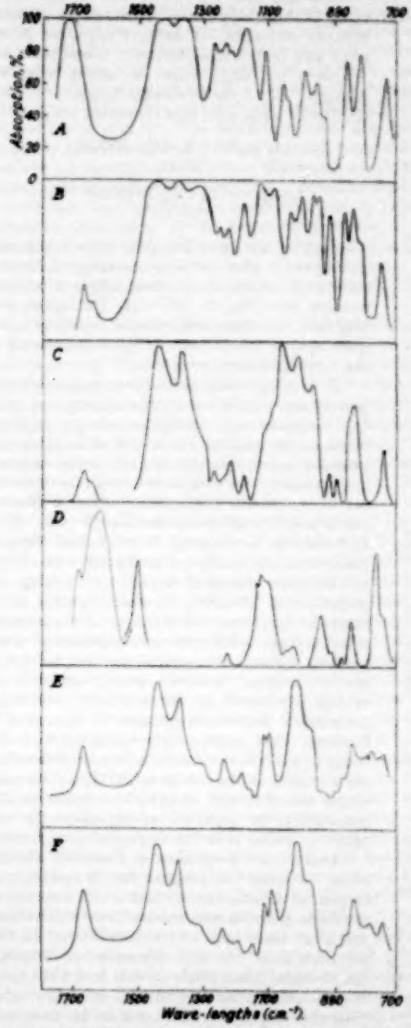
$(CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot})_2$ (XI.)

$(CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot})_2O$ (XII.)

Crystalline geranylamine hydrochloride (VI; X = NH$_3$Cl) is notable in showing very strong absorption at 888 cm.$^{-1}$ (see Fig. 3) although the presence of the hypothetical *iso*propenyl isomer has been excluded by Jeffrey's (*loc. cit.*) complete *X*-ray structure analysis. The readily crystallised homogeranamide (VI; X = CO·NH$_2$) also exhibits a rather large band in this spectral region (see Fig. 2), but this again cannot be attributed to the presence of *iso*propenyl groups since the corresponding liquid acid (VI; X = CO$_2$H) from which it was made showed no such absorption.

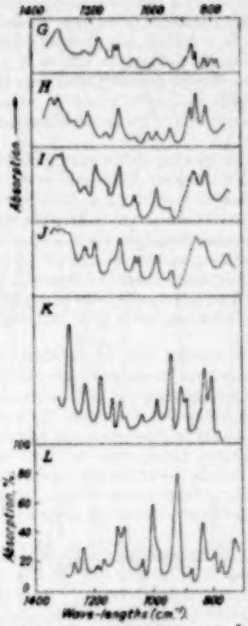
Elimination of the $-CH_2{\cdot}OH$ grouping from geraniol results in the *iso*propenyl structure (V; X = H), which is the main constituent of geraniolene. The intense 890-cm.$^{-1}$ absorption

FIG. 1.



A, *Methylheptenone* (VII) (0·06-*mm. cell*). B, *Methylheptenol* (VIII) (0·06-*mm. cell*). C, *Citronellol "C"* (IX) (0·04-*mm. cell*). D, *Citronellal semicarbazone* (X; X = N·NH·CO·NH_2) (*in "Nujol"*). E, *Geraniol* (trans-VI; X = OH) (0·03-*mm. cell*). F, *Nerol* (cis-VI; X = OH) (0·03-*mm. cell*).

FIG. 2.



G, *Geranamide* I (trans-V; X = CO·NH_2) (*in "Nujol"*). H, *Geranamide* II (cis-V; X = CO·NH_2) (*in "Nujol"*). I, *Geranamide* I (20% *in* CS_2; 0·25-*mm. cell*). J, *Geranamide* II (20% *in* CS_2; 0·25-*mm. cell*). K, *Homogeranamide* (VI; X = CO·NH_2) (*solid*; 0·015 *mm. approx.*). L, *isoHomogeranamide* (XIV; X = CO·NH_2) (0·015-*mm. cell*).

of this hydrocarbon has already been referred to in the table of extinction coefficients (p. 917), as well as in the earlier paper by Sheppard and Sutherland (*loc. cit.*, 1947). A strong band at 890 cm.$^{-1}$ is also known to occur in the spectrum of " dihydromyrcene " obtained by sodium–ethanol reduction of natural myrcene (Sheppard and Sutherland, *loc. cit.*; Thompson and Whiffen, *loc. cit.*), where it arises from the presence of 2-methyl-6-ethylhepta-2 : 6-diene (XIII) (cf. Simonsen and Owen, *op. cit.*).

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CEt{:}CH_2$$
(XIII).

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMeX{\cdot}CH{:}CH_2$$
(XIV.)

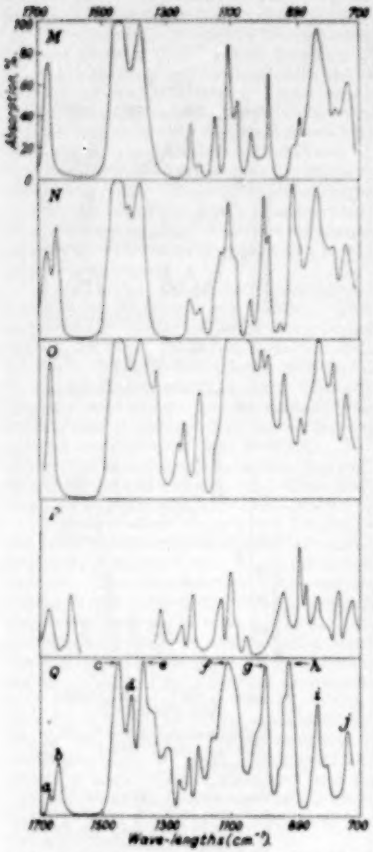
Finally, we have failed to detect any sign of 890-cm.$^{-1}$ absorption in samples of linalool (XIV; X = OH) from two different natural sources (see Fig. 3) (cf. also Thompson and Whiffen), so that this terpene alcohol is unquestionably more than 99% homogeneous in the *iso*propylidene form.

It is clear from the above approximately quantitative infra-red characterisation of purified samples of methylheptenone, methylheptenol, citronellol, citronellal semicarbazone, geraniol, nerol, linalool, the two stereoisomeric geranamides, and certain other synthetic derivatives of geraniol, that none of these substances could possibly contain more than 2—3% of the hypothetical *iso*propenyl isomers, and some of them certainly contain considerably less. Much of the older chemical evidence indicating the presence of 15—50% of such isomers must therefore be deemed unreliable. Furthermore, since certain authentic non-*iso*propenyl compounds display absorption in the 890-cm.$^{-1}$ spectral region, it would seem reasonable to extrapolate most of the observed maximum permissible isomer percentages to zero, and to conclude that *iso*propenyl end-groups do not occur at all in natural acyclic monoterpenes but are confined to the cyclic series (*e.g.*, limonene) where the different structural conditions can reasonably be expected to stabilise the *iso*propenyl relative to the *iso*propylidene forms.

Analytical Significance of Chemical Purification.—During the preparation or isolation of terpenoid substances for infra-red analysis of the *iso*propenyl isomer content, two interrelated problems arise and will be considered in this section: how far the presence of terminal double-bond absorption at 890 and 1645 cm.$^{-1}$ may be attributed to a foreign impurity other than the *iso*propenylic isomer to be detected; and how far on the other hand the isomer in question may escape detection owing to its previous removal as an " impurity " during a rigorous purification.

Experience with such relatively low-boiling *iso*propylidene–*iso*propenyl mixtures as that of 2-methylpent-2-ene with 2-methylpent-1-ene (see Experimental) shows that even with the use of modern packed laboratory fractionating columns it would be extremely difficult to achieve

FIG. 3.



M, *Digeranyl* (XI) (0·1-*mm. cell*). N, *iso*Digeranyl (XV) (0·1-*mm. cell*). O, *Digeranyl ether* (XII) (0·1-*mm. cell*). P, *Geranylamine hydrochloride* (trans-VI; X = NH_3Cl) (*in " Nujol "*). Q, *Linalool* (XIV; X = OH) (0·04-*mm. cell*); a >C:CH·; b $:CH_2$; *c* C–H; *d* $:CH_2$; *e* $\cdot CH_2\cdot$; *f* >C·OH; *g* and *h* $\cdot CH{:}CH_2$; *i* >C:CH·; *j* C·C·C·C·C.

effective separation of terpenoid isomers of this type in a single distillation. Except for citronellol, all terpene samples for infra-red examination were distilled in ordinary Vigreux or spiral columns, and hence there can be no question of the possible removal of *iso*propenyl forms during distillation. In particular, the methylheptenone obtained directly by alkaline cleavage of commercial citral followed by simple fractionation through a short Vigreux column proved constant-boiling and spectroscopically identical with a special sample regenerated from the pure crystalline semicarbazone. The reported homogeneity of this ketone must therefore refer to the entire bulk of the material prepared from natural sources, and not only to some chemically isolated fraction of it. The same conclusion applies to our samples of linalool which had been ordinarily distilled without passing through a crystalline derivative, and also to geraniol isolated from the calcium chloride adduct; the spectrum of the latter alcohol was identical with that of a special sample regenerated from the crystalline diphenylurethane. The same calcium chloride method had been used in the purification of the geraniol which behaves on oxidation as if it contained some 20% of the *iso*propenyl isomer. Similarly, it is the crystalline citronellal semicarbazone of sharp melting point identical with that of our own homogeneous sample which affords ambiguous results by chemical degradation. There can be no doubt, therefore, that the samples investigated by us are truly representative of the compounds described in the chemical literature.

As already indicated, some trouble was experienced in obtaining reasonably pure specimens of citronellol from commercial sources; similar difficulties were evidently encountered by Thompson and Whiffen who have published spectrograms for two different grades of citronellol revealing different absorption intensities at the 890- and 1645-cm.$^{-1}$ bands. In view of the rather wide boiling and refractive index range of our crude samples (which also displayed somewhat strong absorption at these characteristic frequencies), we believe foreign impurities possessing terminal double bonds rather than the *iso*propenyl isomer of citronellol to have been present. The main citronellol fraction selected as a representative sample of the pure compound had very low terminal double-bond absorption and physical constants identical with those given for pure citronellol by Simonsen and Owen (*op. cit.*).

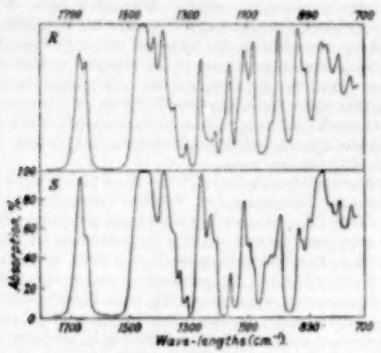
In their specimens of dimethyloctadiene (VI; X = H) obtained by the sodium–liquid ammonia reduction of geraniol, Thompson and Whiffen suspected the presence of an impurity containing vinyl groups, $CHR{:}CH_2$, because variable infra-red absorption occurred at 910, 990, and 1645 cm.$^{-1}$. In our own pure samples of this hydrocarbon (cf. Sheppard and Sutherland, *loc. cit.*, 1947), 910-cm.$^{-1}$ absorption was always small, and there was never any sign of 1645-cm.$^{-1}$ absorption which would be required by the presence of either vinyl or *iso*propenyl groupings. We see no reason to doubt, therefore, that chemically pure dimethyloctadiene from geraniol is a structurally homogeneous compound; on the other hand, it is possible and indeed probable that vinyl groups may be formed on autoxidation, which may account for the variable 910-cm.$^{-1}$ band intensities reported by Thompson and Whiffen.

Terpenoid Compounds containing Vinyl Groups.—The spectra of all the substances hitherto described exhibit certain common characteristic frequencies due to the presence of methyl (1370—1380 cm.$^{-1}$), saturated methylene (1450 and 735—745 cm.$^{-1}$), and *iso*propylidene or other $CHR{:}CR'R''$ (825—845 and 1665—1675 cm.$^{-1}$) groupings. Additional strong bands at 925, 997, 1415, and 1645 cm.$^{-1}$ arise in the spectrum of linalool (XIV; X = OH) (Fig. 3) where a vinyl group is present. The particularly intense 925- and 997-cm.$^{-1}$ absorptions obviously represent the out-of-plane vinyl C–H deformation frequencies which are normally found nearer 910 and 990 cm.$^{-1}$ in hydrocarbons. We have been able to observe similar band displacements in a variety of other allylic functional derivatives of vinyl hydrocarbons (see also below). As a general rule, in a molecule $CH_2{:}CH{\cdot}CRR'X$, where R may be either hydrogen or alkyl, but X represents a functional group, the 908—913-cm.$^{-1}$ hydrocarbon frequency is increased to 918—930 cm.$^{-1}$ (cf. Thompson and Torkington, *Trans. Faraday Soc.*, 1946, **42**, 432; Bateman *et al.*, *J.*, 1950, 936), whereas the 990-cm.$^{-1}$ frequency remains more or less constant when R = R′ = H, but is increased to 995—1005 cm.$^{-1}$, even in hydrocarbons (X = R), when the saturated carbon atom is fully substituted. The latter effect may be explained in terms of increased electron density at the nearer vinyl carbon atom resulting from the extensive substitution (cf. Sheppard and Sutherland, *loc. cit.*, 1949), but the reason for the marked shift in the 910-cm.$^{-1}$ frequency is not at present understood. The 1415- and 1645-cm.$^{-1}$ bands in the linalool spectrum are normal characteristic frequencies of vinyl groups in hydrocarbons, being associated respectively with an in-plane deformation of the terminal methylene group and the stretching of the double bond.

When the hydroxyl group of linalool or geraniol is replaced by halogen, the same halide is

formed which is not constant-boiling (cf. Ruzicka, *Helv. Chim. Acta*, **1923**, **6**, 499; Sutton, *loc. cit.*) and has frequently been suspected of consisting of an anionotropic mixture of (VI) and (XIV; X = Hal) (cf., *e.g.*, Karrer and Helfenstein, *Helv. Chim. Acta*, **1930**, **14**, 78), although positive proof of structure has never been obtained. These compounds are generally referred to simply as " geranyl " halides. In view of the practical and theoretical interest of the structural problem, we have carried out a careful low-pressure fractional distillation (bath temperature <70°) of freshly prepared geranyl chloride and subjected the resulting four fractions to immediate infra-red analysis. The experiment clearly shows that geranyl chloride as originally obtained is mainly (VI), with a small proportion of the lower-boiling tertiary form (XIV). Allylic chlorides of this type exemplify those moderately mobile anionotropic systems in which the isomeric constitution of the isolated product is governed both by the nature of the reaction introducing the mobile atom or group and by the facility of isomeric interconvertibility under the conditions of reaction and isolation (Catchpole, Hughes, and Ingold, *J.*, **1948**, 8). Comparison with simpler allylic halides (*loc. cit.*) indicates that the linaloyl isomer occurs in ordinarily isolated " geranyl chloride " to considerably greater extent than its thermodynamic equilibrium proportion (*ca.* 1%), and in agreement with this fact prolonged heating at a moderate temperature (*ca.* 60°) gives a more homogeneous product.

FIG. 4.



R, *Geranyl chloride (first fraction)* (VI *and* XIV; X = Cl) (0·1 *mm. cell*). S, *Geranyl chloride (last fraction)* (VI *and* XIV; X = Cl) (0·1 *mm. cell*).

The spectra (Fig. 4) of the first and last fractions from the distillation of geranyl chloride are recorded in the figures. The highest-boiling fraction consists essentially of the primary chloride (VI), with strong absorption at 845 and 1665 cm.$^{-1}$, but the small band at 925 cm.$^{-1}$ and the shoulder at 1645 cm.$^{-1}$ indicate the presence of traces of tertiary chloride incorporating a vinyl group in the molecule. In the successively lower-boiling fractions, the 845- and 1665-cm.$^{-1}$-band strengths become gradually reduced, whereas the 925- and 1645-cm.$^{-1}$ bands are greatly intensified; at the same time, existing strong absorption at 988 cm.$^{-1}$ acquires additional intensity, and a new peak appears at 1415 cm.$^{-1}$. The interpretation of these changes in terms of increasing relative amounts of tertiary chloride incorporating the vinyl group is obvious. Other intensity changes occur simultaneously with those of the characteristic bands; in particular, the primary geranyl form appears to be associated with very intense absorption at 1255 cm.$^{-1}$, and the tertiary linaloyl form with a similarly strong band at 1080 cm.$^{-1}$. In view of the markedly different extinction coefficients of vinyl and trialkyl-substituted types of double bond, the spectrum of the lowest-boiling fraction indicates that even here the higher-boiling geranyl form predominates. It may be noted that the usual 910-cm.$^{-1}$ frequency of the vinyl group is again displaced to 925 cm.$^{-1}$; in allyl chloride itself, we observed the characteristic vinyl frequencies at 930, 985, 1415, and 1645 cm.$^{-1}$.

Two structurally isomeric hydrocarbons are produced during the coupling reaction of geranyl chloride over magnesium (Barnard and Bateman, *J.*, 1950, 932). The straight-chain digeranyl (XI) (with a very small band at 908 cm.$^{-1}$ probably due to a trace of the isomer) has

already been referred to above; the structure of the branched-chain *iso*digeranyl (XV) is clearly characterised by intense vinyl absorption peaks at 908, 998, and 1642 cm.$^{-1}$, as well as a smaller

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe(CH{:}CH_2){\cdot}CH_2{\cdot}CH{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CMe_2$$
(XV.)

band at 1415 cm.$^{-1}$ (Fig. 3). The slight but significant increase in the usual 990-cm.$^{-1}$ frequency of the vinyl group to 998 cm.$^{-1}$ in this hydrocarbon can probably be attributed to the inductive effect of the three alkyl substituents at the adjacent carbon atom, as suggested above. *iso*Homogeranamide (XIV; X = CO·NH$_2$) similarly displays vinyl absorption at the displaced frequencies of 920 and 1005 cm.$^{-1}$ (Fig. 2).

Stereoisomerism.—In accordance with certain chemical evidence (Simonsen and Owen, *op. cit.*) and the known structure of the derived amine hydrochloride (Jeffrey, *loc. cit.*), geraniol (VI; X = OH) is believed to be the *trans*-isomer • with respect to the ambiguous configuration of the double bond adjacent to the primary alcohol grouping. The stereoisomeric nerol (*cis*-VI; X = OH) shows only minor differences of infra-red absorption, as might be expected from the general similarity of the two structures. The same kind of *cis-trans*-isomerism about a trisubstituted ethylenic linkage exists in the two 3-methylpent-2-enes where, again, relatively little, but nevertheless distinct, differentiation of infra-red spectra has been reported (A.P.I., *op. cit.*). We have also observed slight differences of infra-red absorption between the two isomorphous crystalline diphenylurethanes of geraniol and nerol. The *cis-trans*-isomeric geranamides (V; X = CO·NH$_2$) were crystallographically distinct from each other (Dr. G. A. Jeffrey, private communication) and the accompanying diagrams show that their infra-red spectra were more highly differentiated for the crystalline substances than they were for solution.

C–O *Frequencies of Terpenoid Alcohols.*—It appears to be generally true that saturated primary, secondary, and tertiary aliphatic alcohols display intense absorption at 1040—1080, 1100—1130, and 1160—1200 cm.$^{-1}$ respectively (cf. A.P.I., *op. cit.*; Sexton and Britton, *J. Amer. Chem. Soc.*, 1948, **70**, 3606), arising from the stretching vibration involving the C–O bond. The strong bands of the primary citronellol (IX) at 1055 cm.$^{-1}$ and of the secondary methylheptenol (VIII) at 1120 cm.$^{-1}$ are in line with this classification, but the characteristic frequencies of the allylic alcohols geraniol and nerol (VI; X = OH) at 1010 and of linalool (XIV; X = OH) at 1115 cm.$^{-1}$ are below the range assigned to their primary or tertiary class. Since allyl alcohol itself exhibits a similar shift of the alcohol band to 1027 cm.$^{-1}$ (Thompson and Torkington, *loc. cit.*, 1946), these low-frequency displacements appear to arise from the presence of the double bond in the allyl position and may be associated with a lowering of the force constant of the C–O bond in allylic environment. The characteristic ether absorption of digeranyl ether (XII) near 1080 cm.$^{-1}$ likewise occurs below that commonly observed above 1100 cm.$^{-1}$ in saturated primary ethers, and the displacement may again be ascribed to an allylic structural effect (for comparative data, cf. Barnes *et al.*, *Ind. Eng. Chem. Anal.*, 1943, **15**, 659).

The infra-red measurements were initiated at Cambridge, later continued by courtesy of the Directors at the Research Department of Messrs. Imperial Chemical Industries, Ltd. (Plastics Division), where facilities were kindly provided by Mr. H. A. Willis, and finally completed at the B.R.P.R.A. laboratories with valuable assistance from Miss J. M. Fabian. The work described forms part of a programme of fundamental research undertaken by the Board of the British Rubber Producers' Research Association.

(D. B., L. B., AND H. P. K.) BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
48 TEWIN ROAD, WELWYN GARDEN CITY, HERTS.
(A. J. H., N. S., AND G. B. B. M. S.) LABORATORY OF COLLOID SCIENCE,
CAMBRIDGE. [*Received, September 16th*, 1949.]

• We have adopted the general convention recently recommended by the Nomenclature Committee of the American Chemical Society (*Chem. Eng. News*, 1949, **27**, 1303), according to which geraniol is derived from *trans*-octadiene and should therefore be correctly formulated as 3 : 7-dimethylocta-*trans*-2 : 6-dien-1-ol. This convention seems both logical and in harmony with the universal practice of describing the two stereoisomeric polyisoprenes rubber and gutta-percha as *cis*- and *trans*-isomers respectively. Unfortunately, some confusion exists in the literature as many authors (*e.g.*, Simonsen and Owen, *op. cit.*; Caldwell and Jones, *loc. cit.*) have rather arbitrarily referred to geraniol and its derivatives as *cis*-isomers.

187. *Experiments relating to the Synthesis of Homogeranic Acid.*

By D. Barnard and L. Bateman.

Homogeranic acid (I; X = CO_2H) is obtained only in poor yield from *geranoyl chloride* by the Arndt–Eistert synthesis, and the production of the corresponding *cyanide* from geranyl chloride and cuprous cyanide is similarly inefficient. However, a novel and general method for synthesising allylic cyanides, *viz.*, allyl halide ⟶ allylmalonic ester ⟶ α-oximinoallylacetic acid ⟶ allyl cyanide, renders geranyl cyanide, and thence homogeranic acid, readily accessible. 1- and 3-Methylallyl cyanide and the hitherto difficultly obtainable cinnamyl cyanide have been prepared from the respective chlorides by the above method. The product from the condensation of 1-methylallyl chloride with sodiomalonic ester contains a small proportion of *3-methylallylmalonic* ester; the relation of this finding to the S_N2' mechanism of allylic halide replacement (Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185) is discussed.

Although no previous attempt to apply the Arndt–Eistert process

$$R{\cdot}CO_2H \longrightarrow R{\cdot}COCl \longrightarrow R{\cdot}CO{\cdot}CHN_2 \longrightarrow R{\cdot}CH_2{\cdot}CO_2H$$

to aliphatic αβ-unsaturated acids is on record, the successful conversion of several aromatic acids into substituted acetic acids and of an alicyclic βγ-unsaturated acid into the corresponding γδ-unsaturated acid by this method ("Organic Reactions", Wiley and Sons, N.Y., 1942, Vol. I, pp. 38 *et seq.*) gave reason to believe that the synthesis of homogeranic acid (I; X = CO_2H) from geranic acid (II; X = OH) could be realised without difficulty.

The first intermediate, *geranoyl chloride* (II; X = Cl), has not been described hitherto, but is readily prepared in good yield from the acid and thionyl chloride in the presence of pyridine, if particular care is exercised in purifying the thionyl chloride. Interaction of (II; X = Cl) with aqueous ammonia yields a geranamide (II; X = NH_2) mixture separable by fractional elution from alumina into two crystalline isomers. These are the compounds designated as geranamide-I and geranamide-II, respectively, by Caldwell and Jones (*J.*, 1946, 599), who first isolated them as rearrangement products from the action of Raney nickel on citral oxime. Comment on the structure of the compounds in the light of their infra-red spectra is made elsewhere (Barnard *et al.*, preceding paper). Notwithstanding the distinct preparative routes, the isolated mixtures contained the same relative proportion of isomers (5 : 1).

$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2X$ (I.) $\qquad$ $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO{\cdot}X$ (II.)

$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMeX{\cdot}CH{:}CH_2$ (III.)

The second stage of the projected synthesis also proceeds normally, to yield the liquid *diazomethyl* 2 : 6-*dimethylhepta*-1 : 5-*dienyl ketone* (II; X = CHN_2). The final stage, however, proved decidedly abnormal. Repeated attempts to rearrange the diazo-ketone to homogeranic acid (I; X = CO_2H) or to homogeranamide (I; X = $CO{\cdot}NH_2$) under the usual conditions using colloidal silver as catalyst gave only tar and much residual diazo-ketone. The possible catalytic activity of a variety of metallic compounds was then investigated. Although auric chloride proved to be an active catalyst for promoting the decomposition of the diazo-ketone in ethanol at room temperature, complex side-reactions greatly preponderated and, on hydrolysis, only 7% of *homogeranic acid* (I; X = CO_2H) was obtained.

Diazomethyl 2 : 6-dimethylhepta-1 : 5-dienyl ketone clearly possesses unusual stability, as is further emphasised by the fact that it can be distilled without appreciable decomposition at 0·05 mm. pressure from a bath at 100° (b. p. 87—88°). Although many diazo-ketones possess comparable thermal stability, few are resistant to the usual rearrangement procedures. The several indefinite interpretations of the mechanism of the rearrangement that have been propounded certainly offer no indication of any special function of the alkenyl substituent in the present example.

The limited success achieved forced our attention to preparative methods based on geranyl chloride. An inherent disadvantage of this approach is the possibility of allylic isomerism. This complication intrudes in three ways: (i) possible inhomogeneity of the terpenoid starting material or of an intermediate; (ii) similar inhomogeneity of the desired product even if its precursor were pure; and (iii) the analytical problem of identifying and characterising various isomers. The last of these, clearly of dominant importance, is now greatly facilitated by recent developments in the recording and interpretation of infra-red spectra (see Barnard *et al.*, *loc. cit.*).

Pure geraniol is entirely the primary allylic alcohol (I; X = OH). On treating it with

thionyl chloride and pyridine (Forster and Cardwell, *J.*, 1913, 1341), a product boiling over a range of about 20° is obtained (cf. Ruzicka, *Helv. Chim. Acta*, 1923, **6**, 492; Sutton, *J.*, 1944, 306), which gives analyses correct for the derived chloride and which infra-red spectroscopic analysis reveals to be a mixture of the primary (geranyl) (I; X = Cl) and the tertiary (linaloyl) (III; X = Cl) chloride in the ratio of roughly 5 to 1.* Separation of the isomers by fractionation is extremely difficult because of decomposition during the prolonged heating at the relatively high temperature needed. More rapid distillation at the lowest convenient pressure (*ca.* 0·2 mm.) effects some separation, the tail portions consisting of almost pure primary chloride. However, for reasons which will emerge, the use of the pure isomers offers no advantage in the present work.

Recent work by Lane, Fentress, and Sherwood (*J. Amer. Chem. Soc.*, 1944, **66**, 545) indicated that the conversion of an allylic halide into the carboxylic acid homologue *via* the nitrile offered not only the most direct, but a most favourable structural, route to homogeranic acid. These authors showed that the simpler analogues of the constituents of the geranyl chloride mixture, *viz.*, 1- and 3-methylallyl chloride, interact with cuprous cyanide so that, independently of the nature of the pure halide or of the composition of an isomeric mixture, the same equilibrium mixture of cyanides is formed (91·5% of crotyl, 8·5% of 1-methylallyl). Furthermore, when the mixture is hydrolysed by acid, the 1-methylallyl constituent behaves abnormally and the isolated acid is derived solely from the crotyl isomer. Once again, however, the extension to di-isoprenic derivatives of a method successful with simpler analogues was disappointing. Under the experimental conditions of Lane *et al.* (*loc. cit.*) and modifications thereof, the maximum yield of *geranyl cyanide* was no more than 11%, in marked contrast to the approximately 90% conversion obtained in the methylallyl system. As expected, isomeric heterogeneity of the product was indicated by a boiling range of 7° (cf. geranyl chloride), but in addition it appeared to be very slightly impure. Although this synthesis is therefore of little preparative value in the geranyl series, the present work corroborates the American authors' important findings concerning the formation of homogeneous hydrolytic products from isomeric mixtures of allylic nitriles. Alkaline hydrolysis converted the above geranyl cyanide into homogeneous homogeranic acid (I; X = CO_2H), which in turn has been converted *via* its *acid chloride* into crystalline *homogeranamide*, identical in melting point and infra-red spectrum with a specimen prepared from homogeranic acid isolated from the rearrangement of diazomethyl 2 : 6-dimethylhepta-1 : 5-dienyl ketone. A similarly identical specimen is obtained directly from the cyanide on mild hydrolysis with alkaline hydrogen peroxide, thus establishing that no double-bond displacement occurs during the relatively severe hydrolysis of the cyanide. The ultra-violet absorption spectrum also proves the absence of αβ-unsaturated conjugation in the acid.

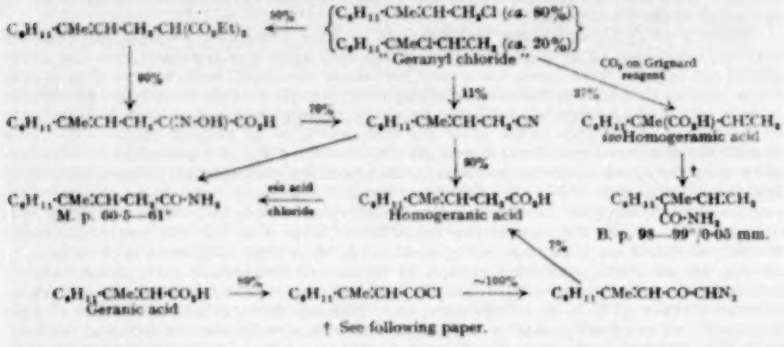
At this stage, when the possibility of finding an improved route to homogeranic acid seemed remote—especially as we had found in the meantime that carboxylation of geranylmagnesium chloride yields the tertiary allylic derivative (III; X = CO_2H) (see following paper)—Barry and Hartung (*J. Org. Chem.*, 1947, **12**, 460) described preparations of α-oximino-acids. One method involves a novel transformation of alkylmalonic esters. On treatment with an alkyl nitrite in alkaline solution, efficient oximation of these esters at the tertiary carbon atom is accompanied by simultaneous hydrolysis and decarboxylation of one carbethoxyl group, *i.e.*, $CHR(CO_2Et)_2 \longrightarrow HO{\cdot}N{:}CR{\cdot}CO_2H$. Now it is known that α-oximino-acids, while resistant to alkaline hydrolysis, tend to lose water and carbon dioxide in strongly acid solution with the formation of nitriles containing one less carbon atom (Bouveault and Loquin, *Bull. Soc. chim.*, 1904, **31**, 1142). Yields of the nitriles thus obtained are generally poor, and, in any case, the extension of this reaction to open-chain terpenoid compounds is restricted by the sensitivity of the latter towards mineral acids, but it seemed reasonable to expect that the mineral acid could be replaced with advantage by a powerful dehydrating agent. Experiment confirmed this; the addition of acetic anhydride to a solid α-oximino-acid caused almost explosive decomposition, but the use of low-boiling petroleum as a diluent gave a high yield of nitrile.

Ethyl geranylmalonate [I; X = $CH(CO_2Et)_2$] was prepared in 50% yield † by condensing sodiomalonic ester with the geranyl chloride mixture (cf. above) and was structurally homogeneous (see below); with amyl nitrite it gave *α-oximinogeranylacetic* (*1-oximino-4 : 8-dimethyl-n-deca-3 : 7-dienoic*) *acid* [I; X = $C(:NOH){\cdot}CO_2H$] in 90% yield. On crystallisation from aqueous

* This ratio is determined by the conditions of reaction and of subsequent isolation; it is not to be regarded as reflecting the free-energy difference between the isomers.

† The yields in this and the analogous condensations referred to later are typical for the experimental conditions employed; they may not be the highest possible.

acetone, metastable and stable forms were obtained (presumably *syn*- and *anti*-oxime isomers): the former reverted readily to the latter on subsequent recrystallisation. Smooth decomposition ensued on adding acetic anhydride to a suspension of this acid in light petroleum. The product, isolated in 70% yield, was homogeneous and analytically pure (cf. p. 927), and yielded derivatives identical with those prepared from the geranyl cyanide which had been synthesised much less satisfactorily from cuprous cyanide and geranyl chloride. The annexed reaction scheme summarises the inter-relationships of the compounds studied and records the yields of those reactions of preparative significance.



† See following paper.

The alkylated malonic ester route to cyanides provides a new method for ascending a homologous series which is especially useful for fairly reactive halides. The difficulty experienced with direct halide–cyanide exchange in these cases arises from the fact that the cyanide ion is too weak a base to initiate a bimolecular (S_N2) reaction which can compete successfully with solvolysis of the halide by the hydroxylic solvent, whose presence is demanded by solubility considerations. The heterogeneous cuprous cyanide system introduces other factors which may, or, as with geranyl chloride, may not, contribute to successful interaction. The ethyl malonate anion is not only a sufficiently powerful base to engage in effective nucleophilic attack in a hydroxylic medium, but also yields a product of unique functional character. To test the response of other allylic compounds to this synthesis, the conversion of cinnamyl chloride and of 1- and 3-methylallyl chloride into the respective cyanides has been investigated.

Ethyl cinnamylmalonate reacted with n-butyl nitrite in alkaline ethanol to give *α-oximinocinnamylacetic* (*1-oximino-4-phenylpent-3-enoic*) *acid* (83%). This acid is dehydrated and decarboxylated extremely easily. Even repeated recrystallisation from aqueous ethanol suffices to effect complete conversion into cinnamyl cyanide, although this is effected more expeditiously in bulk by treating a light-petroleum suspension with acetic anhydride as described previously. The one preparation of this nitrile recorded (Borsche and Niemann, *Ber.*, 1936, **69**, 1993) gives a poor yield. Hydroiysis of the nitrile with alcoholic potash yielded 79% of the expected phenylisocrotonic acid, Ph·CH:CH·CH$_2$·CO$_2$H (Buchner and Dessaver, *Ber.*, 1892, **25**, 1155; Fittig and Jagne, *Annalen*, 1883, **216**, 98).

Ethyl (*1-methylallyl*)*malonate* and crotylmalonate (cf. Eccott and Linstead, *J.*, 1929, 2153, and Linstead and Rydon, *J.*, 1934, 1995) were prepared from the respective chlorides in >50% yields. Since Linstead *et al.*'s samples of crotyl bromide were unquestionably heterogeneous (Winstein and Young, *J. Amer. Chem. Soc.*, 1936, **58**, 104), some doubt exists concerning the purity of these products, but, for reasons referred to below, contamination with the 1-methylallyl isomer was probably inappreciable. To free the derived esters from traces of ethyl malonate, however, very careful fractionation was necessary. The purified esters were transformed in the usual way into 1-oximino-2-methylpent-3-enoic and 1-oximinohex-3-enoic acid, crystalline solids, which were dehydrated directly in ethereal solution without isolation. The cyanides were obtained in high yield, were apparently homogeneous, and exhibited physical constants in close agreement with those reported by Lane, Fentress, and Sherwood (*loc. cit.*), but were found to evolve hydrogen cyanide on distillation and were therefore not obtained analytically pure. The

cause of this slight decomposition (possibly an impurity) was not further investigated as the synthetic route was considered to be sufficiently demonstrated.

Certain further observations on the sodiomalonic ester condensations deserve mention. First, 1-methylallyl chloride reacts much more slowly than its 3-methyl isomer, in accord with the quantitative data of Young and Andrews (*J. Amer. Chem. Soc.*, 1944, **66**, 421) and of Catchpole and Hughes (*J.*, 1948, 4) on the related bimolecular substitutions with ethoxide ions. Since these authors have also established that the halides undergo unimolecular solvolysis at similar rates, it follows that under conditions where both modes of halide replacement occur the production of the primary allylic malonic ester is favoured. This is undoubtedly the principal reason why the geranyl chloride (p. 928) and crotyl bromide (p. 928) mixtures yield products containing inappreciable proportions of the secondary allylic derivative. Secondly, while the malonic ester isolated from 3-methylallyl chloride possessed *entirely* the allylic structure of the parent halide, in the 1-methylallyl series this was only *mainly* so. From the crude (1-methylallyl)malonic ester was separated a small amount of a mixed ester fraction, the analysis of which indicated that about 3% of the 3-methylallyl isomer had been formed. From such product composition data alone, it is impossible, of course, to draw conclusions about the reaction mechanism, but this finding suggests the operation of the long-forecast (Hughes, *loc. cit.*), but experimentally elusive (cf. Catchpole, Hughes, and Ingold, *J.*, 1948, 8), S_N2' reaction :

During the preparation of this paper, Kepner, Winstein, and Young (*J. Amer. Chem. Soc.*, 1949, **71**, 115) reported an investigation designed expressly to detect the S_N2' mechanism if operative in the reactions just considered and in the analogous condensations with 1- and 3-ethylallyl chloride. The composition of the derived malonic esters was not examined directly; instead, these were successively hydrogenated, hydrolysed, and decarboxylated, the resulting straight-chain saturated acids fractionated, and the distillates converted in portions into the benzylamine salts, whose isomeric compositions were ascertained by melting-point comparisons. By this laborious procedure, applied apparently to a single experiment, the product obtained from 1-methylallyl chloride in boiling ethanol was found to contain $10 \pm 3\%$ of 3-methylallylmalonic ester—an estimate in reasonable agreement with our value based on partial separation and analytical identification of the rearranged ester, which also refers to one experiment and is probably somewhat low. With 1-ethylallyl chloride, rearrangement occurs to a greater extent ($23 \pm 3\%$), and this is attributed to decreased S_N2 reactivity arising from increased steric hindrance to the approach of the malonate ion at the α-carbon atom. In the tertiary allylic (linalyl) chloride (III; X = Cl), this steric situation is greatly emphasised and will be an additional factor contributing to the formation of homogeneous geranylmalonic ester [I; $X = CH(CO_2Et)_2$] from the isomeric chloride mixture (cf. above). By accessory rate measurements, Kepner *et al.* further showed (i) that the condensation is a bimolecular reaction, of the first-order with respect to both allyl chloride and malonate ion, and (ii) that it proceeds much faster than unimolecular solvolysis of the chloride. On this evidence, they naturally deduce that the production of the rearranged ester from the 1-alkylallyl chlorides definitely establishes the existence of the S_N2' mechanism.

Experimental.

The absence of selective infra-red absorption at the frequencies 910 and 990, 965, and 835 cm.$^{-1}$, or at small recognisable displacements therefrom, is taken as characterising the absence of $CH_2{:}CHR$, *trans*-CHR:CHR′, and $CRR''{:}CHR''$, respectively. The experimental basis for the analytical use of infra-red spectroscopy in this sense is presented and discussed elsewhere (Barnard *et al.*, *loc. cit.*).

The micro-analyses recorded in this and the following papers were carried out in the Analytical Department of these laboratories under the direction of Dr. W. T. Chambers.

Geranic Acid.—Oxidation of commercially pure citral by alkaline silver oxide, essentially according to Semmler's directions (*Ber.*, 1890, **23**, 3556), gave a product (65%) which after careful fractionation had b. p. 99—100°/0·1 mm., n_D^{20} 1·4876.

Geranoyl Chloride.—Distilled thionyl chloride with geranic acid in the presence of pyridine gave much tar and practically none of the desired product. However, by the use of specially purified thionyl chloride under the same conditions, good yields were readily obtained. To an ice-cooled and stirred mixture of

geranic acid (50 g.), anhydrous pyridine (23·7 g.), and anhydrous ether (150 ml.) was slowly added thionyl chloride (28·7 ml.), freshly purified by successive distillation from quinoline and linseed oil. After filtration from the precipitated pyridine hydrochloride, the filtrate was refluxed for 1 hour. Removal of solvent and fractionation of the residue gave *geranoyl chloride* (81%) as a colourless liquid, b. p. 77—78°/0·3 mm., n_D^{25} 1·4963, d_4^{25} 0·9955 (Found: C, 64·6; H, 8·3; Cl, 18·7. $C_{10}H_{15}OCl$ requires C, 64·4; H, 8·1; Cl, 19·0%).

Isomeric Geranamides.—Geranoyl chloride (7 g.), added slowly to stirred 20% aqueous ammonia (15 ml.) at 0°, yielded an oil (5 g.), which was separated into geranamide-I (1·83 g.) and geranamide-II (0·36 g.) by the chromatographic procedure described by Caldwell and Jones (*loc. cit.*). The isomer-I crystallised from light petroleum (b. p. 60—80°) in long needles, m. p. 67·8—68·4° (Found: C, 71·8; H, 10·3; N, 8·3. Calc. for $C_{10}H_{17}ON$: C, 71·8; H, 10·3; N, 8·4%); the amide-II separated from the same solvent in lustrous plates, m. p. 61·6—61·9° (Found: N, 8·5%).

Diazomethyl 2 : 6-*Dimethylhepta*-1 : 5-*dienyl Ketone.*—Geranoyl chloride (45 g.) in ether (150 ml.) was added slowly, with efficient stirring, to a solution of diazomethane (from 139 g. of *N*-nitrosomethylurea) in ether (900 ml.) cooled to −10°. After being kept at 0° for 48 hours and at 20° for 1 hour, the reaction mixture was filtered, and the ether and excess of diazomethane were removed under reduced pressure at 26—28°. The residual diazo-ketone (46 g.) was an orange oil, b. p. 87—88°/0·05 mm., n_D^{25} 1·5395 (Found: C, 69·0; H, 8·6; N, 14·9. $C_{11}H_{16}ON_2$ requires C, 68·7; H, 8·4; N, 14·6%). Light-absorption measurements in ethanol showed intense bands at 2560 (ε = 11,000) and 3060 A. (ε = 10,250).

Rearrangement of Diazomethyl 2 : 6-*Dimethylhepta*-1 : 5-*dienyl Ketone.*—Attempted Wolff rearrangement of the diazoketone in (*a*) aqueous dioxan solution at 55° and 80°, (*b*) aqueous dioxan saturated with ammonia at 60° or under reflux, and (*c*) ethanol saturated with ammonia at room temperature or under reflux, in the presence of silver oxide or colloidal silver, produced only some tar; much unchanged diazo-ketone was recovered. In a wide survey of possible catalysts for the rearrangement of the diazo-ketone as a 10% solution in ethanol, positive promotion (as shown by nitrogen evolution) was found only with silver oxide and colloidal silver (slightly active) and with auric chloride (highly active).

Homogeranic Acid.—To a solution of diazomethyl 2 : 6-dimethylhepta-1 : 5-dienyl ketone (35 g.) in ethanol (400 ml.) and water (20 ml.) at 50°, a saturated solution of auric chloride (0·4 g.) in ethanol was added at such a rate that nitrogen evolution was approx. 30 c.c./min. After gas evolution had ceased, potassium hydroxide (12 g.) was added to the red, turbid solution, which was refluxed for 3 hours, filtered, and evaporated to 100 c.c. under reduced pressure. Water (400 ml.) was added, and the solution extracted with ether and then acidified with concentrated hydrochloric acid (20 ml.). *Homogeranic acid* separated as an oil which, dried (Na_2SO_4) and fractionated, had b. p. 110—110·5°/0·1 mm., n_D^{25} 1·4743 (Found: C, 72·5; H, 9·8%; [α], 1·97 (catalytic hydrogenation). $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·9%; [α], 2·0). Yield, 2·5 g.

Homogeranamide.—Homogeranic acid (2 g.) in ether (3 ml.) was treated with pyridine (1 g.) and thionyl chloride (1·4 ml.) at 0°; after dilution further with ether and filtration, homogeranic acid chloride, b. p. 68—71°/0·1 mm., was obtained by evaporation. Interaction of this chloride with ammonia in ethanol, and isolation of the product in the usual way, gave an oil which rapidly solidified at room temperature. Recrystallisation from light petroleum (b. p. 40—60°) yielded *homogeranamide* as white platelets, m. p. 60·5—61° (Found: C, 72·8; H, 10·6; N, 7·9. $C_{11}H_{19}ON$ requires C, 72·9; H, 10·6; N, 7·8%). Fractional elution from alumina following the procedure used for separating the isomeric geranamides indicated homogeneity of the amide. Its infra-red spectrum indicates that the olefinic unsaturation is of the type $R_2C{:}CHR$.

Geraniol.—"Geraniol Q" (Boake Roberts & Co.), purified through its calcium chloride addition compound and then fractionated, had b. p. 112·5—113·5°/13 mm., n_D^{25} 1·4765. Yield, approx. 60%. Its infra-red spectrum is incompatible with the presence of $CH_2{:}CHR$ groups, and therefore establishes its identity as the homogeneous primary allylic alcohol (I; X = OH).

Geranyl Chloride.—To a mixture of geraniol (200 g.), pyridine (110 g.), and anhydrous ether (200 ml.), thionyl chloride (170 g.) was slowly added with vigorous stirring and ice-cooling (cf. Forster and Cardwell, *loc. cit.*). After being kept for several hours at room temperature, the mixture was stirred with ice-water (3 l.), and the upper layer separated, washed with dilute sodium hydroxide solution until alkaline and then with water, and finally dried ($CaCl_2$). On fractionation through a 35-cm. Vigreux column, the product always exhibited a continuous boiling range, 50—105°/11 mm. or 25—55°/0·2 mm.; only the fraction, b. p. 85—105°/11 mm. or 45—55°/0·2 mm., n_D^{25} 1·4728—1·4790 (beginning and end of fraction), gave correct analytical figures for geranyl chloride (Found: Cl, 20·1—20·5. Calc. for $C_{10}H_{17}Cl$: Cl, 20·6%).

On dividing the chloride during fractionation into several fractions of increasing b. p., it was found by infra-red spectroscopy that the lower-boiling fractions contained considerable amounts of the isomeric tertiary chloride (linalyl chloride; III; X = Cl), the proportion decreasing with increasing b. p. until the fraction of highest b. p. was practically pure primary chloride (I; X = Cl). As is usual with allylic chlorides, the isomeric composition of these fractions changed on long storage or on heating them in a vacuum for a shorter period.

A freshly prepared sample of geranyl chloride, distilled at 0·2 mm. and of the boiling range given above, contains approx. 20% of the tertiary isomer (see footnote p. 927).

Geranyl Cyanide.—On mixing geranyl chloride (54 g.), pyridine (30 g.), and anhydrous cuprous cyanide (30 g.), heat was evolved and a pasty mass resulted; the paste liquefied on raising of the temperature to about 75°. After being maintained at this temperature for 2 hours, and at 100° for 0·5 hour, the dark syrup was poured rapidly into ether. The insoluble matter was separated, washed with ether, and the combined extracts were worked up in the usual way. The main product (30 g.) was a halogen- and nitrogen-free liquid, b. p. 45—87°/0·1 mm., and there was a much smaller amount (5 g.) of material, b. p. 87—94°/0·2 mm. Refractionation of the latter yielded a pleasant-smelling, very pale yellow oil, b. p. 90—91°/0·2 mm., n_D^{25} 1·4701, evidently slightly impure *geranyl cyanide* (Found: C, 79·7; H, 10·5; N, 7·8. $C_{11}H_{17}N$ requires C, 81·0; H, 10·5; N, 8·6%).

Hydrolysis of Geranyl Cyanide.—Geranyl cyanide (5 g.) was refluxed for 6 hours with 20% aqueous ethanol (80 ml.) containing potassium hydroxide (5 g.); no more ammonia was then evolved. The resulting acid (2·6 g.), b. p. 105—9°/0·05 mm., n_D^{20} 1·4744 (Found: C, 72·3; H, 10·0. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 9·9%), was identical with the homogeranic acid previously isolated, and gave, *via* its acid chloride, homogeranamide m. p. 59—59·5°, mixed m. p. 60·0—60·5°.

Geranyl cyanide (3·6 g.) was dissolved in ethanol (20 ml.) containing sodium hydroxide (1 ml.; 6N.), and 30% hydrogen peroxide (9 ml.) was added. Rapid effervescence occurred with the intermediate formation of a crystalline complex which subsequently re-dissolved. The solution was kept at 50° for 4 hours, and a crystalline product (3 g.) then isolated by ether-extraction. Several recrystallisations from light petroleum (b. p. 40—60°) yielded pure homogeranamide, m. p. 60·0—60·5°.

Ethyl Geranylmalonate.—Redistilled ethyl malonate (126 g.) was added during 30 minutes to a hot solution of sodium (17·8 g.) in anhydrous ethanol (750 ml.). Geranyl chloride (138 g.) was then added with vigorous stirring at a rate sufficient to keep the solution gently refluxing. Heating was continued until the mixture was neutral to moist litmus (2 hours), whereafter most of the ethanol was removed by distillation. The oil obtained by pouring the residue into water gave, on fractionation, much low-boiling material together with the desired product (100 g.), b. p. 126—129°/0·2 mm., n_D^{20} 1·4610 (Found: C, 68·9; H, 9·6. Calc. for $C_{17}H_{28}O_4$: C, 68·9; H, 9·5%). The infra-red spectrum indicates the absence of CH_2:CHR groups, and thus identifies the product as a primary allylic geranyl derivative.

α-Oximinogeranylacetic Acid.—Sodium (7·8 g.) was dissolved in ethanol (200 ml.), and ethyl geranylmalonate (100 g.) added slowly at 0°; n-amyl nitrite (43 g.) was then added dropwise with vigorous stirring. After removal of the ethanol under reduced pressure at 30°, the red residue was mixed with crushed ice (130 g.), acidified with 25% aqueous sulphuric acid (100 ml.), and extracted with ether. The ethereal extract was washed with 10% sodium hydroxide solution (6 × 50 ml.) until colourless and the aqueous solution thus obtained heated for 15 minutes on the steam-bath, the dissolved ether being distilled off. On acidification at 0°, a yellow solid (62 g.) was precipitated which was dried in a vacuum. Crystallisation was effected most readily by dissolution in boiling acetone, addition of water to cause slight turbidity, and then storage at 0°. *α-Oximinogeranylacetic* (*1-oximino-4 : 8-dimethyl-n-deca-3 : 7-dienoic*) *acid* was first obtained as colourless platelets, m. p. 138—139°, but the m. p. decreased with successive crystallisations to a constant value of 102·0—102·2°, the crystalline form now being needles (Found: C, 64·0; H, 8·1; N, 6·2%; equiv., 222. $C_{12}H_{19}O_3N$ requires C, 63·9; H, 8·5; N, 6·2%; equiv., 225).

Dehydration of α-Oximinogeranylacetic Acid.—The finely powdered, crude product (87 g.) was suspended in light petroleum (b. p. 60—80°; 200 ml.), and acetic anhydride (100 ml.) added slowly with stirring. Carbon dioxide was smoothly liberated, and the heat of reaction was sufficient to induce gentle boiling. The resulting solution was stirred with water for 2 hours and the undissolved oil worked up in the usual manner and fractionated. The product (43 g.), b. p. 81—82°/0·1 mm., n_D^{20} 1·4698, appeared to be identical with the geranyl cyanide obtained previously (Found: C, 80·8; H, 10·3; N, 8·4%). Hydrolysis with alkaline hydrogen peroxide yielded a crystalline amide, m. p. 60·0—60·5° alone or mixed with the original homogeranamide.

Homogeranic Acid.—Geranyl cyanide, obtained *via* the oximino-acid derivative, was hydrolysed with alcoholic potassium hydroxide solution as described previously, and an acid isolated, in 90% yield, identical with the original homogeranic acid (p. 930), b. p. 110—110·5°/0·1 mm., n_D^{20} 1·4743 (Found: C, 72·4; H, 9·9%). The infra-red spectrum of this acid indicates that olefinic unsaturation is only of the type R_2C:CHR, thus confirming that no shift of the double bond accompanies the hydrolysis. The absence of side reactions during the latter process is further confirmed by the fact that samples of homogeranamide prepared from the acid and by mild hydrolysis of the cyanide exhibited identical light absorption in the ultra-violet region.

Ethyl Cinnamylmalonate.—Under the above experimental conditions, cinnamyl chloride (142 g.) reacted with ethyl sodiomalonate (from 164 g. of ethyl malonate) to give *ethyl cinnamylmalonate* (130 g.), b. p. 137—140°/0·1 mm., n_D^{20} 1·5139 (Found: C, 69·4; H, 7·1. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·3%). Its infra-red spectrum establishes the absence of isomer containing the CH_2:CHR grouping.

α-Oximinocinnamylacetic Acid.—Treatment of ethyl cinnamylmalonate (119 g.) with n-amyl nitrite in the manner already described yielded *α-oximinocinnamylacetic* (*1-oximino-4-phenylpent-3-enoic*) *acid* (73 g.), which crystallised from aqueous ethanol in white needles, m. p. 132—133·5°. On further recrystallisations, the m. p. steadily decreased until ultimately complete conversion into cinnamyl cyanide was realised.

Cinnamyl Cyanide.—Dehydration of crude α-oximinocinnamylacetic acid (67 g.) with acetic anhydride gave cinnamyl cyanide, m. p. 59·1—59·3° (after recrystallisation from aqueous ethanol) (Found: C, 83·8; H, 6·0; N, 9·9. Calc. for $C_{10}H_9N$: C, 83·9; H, 6·3; N, 9·8%).

3-Phenylisocrotonic Acid.—Hydrolysis of cinnamyl cyanide (10 g.) by refluxing it with alcoholic potassium hydroxide solution until ammonia was no longer liberated (24 hours) produced 3-phenylisocrotonic acid (9 g.), m. p. 87—87·5° (after recrystallisation from aqueous ethanol) (Found: C, 74·2; H, 6·3%; equiv., 163. Calc. for $C_{10}H_{10}O_2$: C, 74·1; H, 6·2%; equiv., 162).

Crotonyl Alcohol.—Meerwein–Pondorff–Verley reduction of crotonaldehyde gave a product having b. p. 120·0—120·6°/760 mm., n_D^{20} 1·4295.

1- and 3-Methylallyl Chloride.—Crotyl alcohol (161 g.) was dissolved in anhydrous ether (200 ml.), and purified thionyl chloride (357 g.) slowly added with stirring at 0°. After refluxing for 1 hour the mixture was cooled to 0° and ice-water added. The ethereal layer was separated, washed with sodium carbonate solution until alkaline and then with water, and dried ($CaCl_2$). On careful fractionation through a Fenske-type column, separation of the isomeric chlorides was achieved without difficulty, but gave 1-methylallyl chloride (61 g.), b. p. 63·0—63·9°/759 mm., n_D^{20} 1·4159, and 3-methylallyl chloride (59·6 g.), b. p. 82·9—83·9°/759 mm., n_D^{20} 1·4357.

Ethyl α-3-Methylallylmalonate (*Pent-3-ene-1 : 1-dicarboxylate*).—Ethyl malonate (115 g.) was alkylated with 3-methylallyl chloride (59 g.) in the usual way; the reaction was complete in 4 hours. Fractionation of the product through a 30-cm. Vigreux column at 0·05 mm. gave fractions with steadily

increasing **n**, but the use of an efficient packed column gave, after a small fore-run (7 g.) (mainly ethyl malonate), a homogeneous distillate (77 g.), b. p. 120·0—120·5°/15 mm., n_D^{20} 1·4362 (Found : C, 61·6; H, 8·6. Calc. for $C_{11}H_{18}O_4$: C, 61·7; H, 8·5%). Its infra-red spectrum reveals that olefinic unsaturation is solely of the type RCH:CHR.

Ethyl α-1-Methylallylmalonate (*2-Methylhex-3-ene-1 : 1-dicarboxylate*).—Ethyl malonate (115 g.) was converted into the sodio-derivative and alkylated with 1-methylallyl chloride (61 g.). The reaction proceeded slowly : after refluxing for 10 hours the mixture was still alkaline to moist litmus and an odour of the chloride remained. However, isolation of the product after this time, followed by efficient fractionation, gave the required *malonate* (83 g.), b. p. 113·0—113·6°/16 mm., n_D^{20} 1·4333 (Found : C, 61·6; H, 8·5. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·4%). Infra-red spectroscopic examination showed that the olefinic unsaturation was purely of the type CH_2CHR. Also isolated was a small amount (3 g.) of a higher-boiling fraction, b. p. 115·5—121°/16·5 mm., n_D^{20} 1·4342—1·4354, which could not be purified further by fractionation ; its infra-red spectrum showed it to be a mixture of 3- and 1-methylallylmalonate in the ratio of 3 : 1.

3-Methylallyl Cyanide.—Ethyl α-3-methylallylmalonate (76 g.) was dissolved in sodium ethoxide solution (from 8·2 g. of sodium and 250 ml. of ethanol) and converted into 1-oximinohex-3-enoic acid by the slow addition of n-butyl nitrite (41 g.). The crude crystalline product was dissolved in ether (200 ml.) and dried (Na_2SO_4), and the solution refluxed for 4 hours while acetic anhydride (70 ml.) was slowly added. The product was stirred with water for 1 hour, and the ethereal layer washed successively with sodium carbonate solution and water, dried (Na_2SO_4), and fractionated through a 20-cm. column packed with glass helices. The cyanide (19·6 g.) had b. p. 142·0—143·0°/763 mm., n_D^{20} 1·4220. During the fractionation, a slight evolution of hydrogen cyanide was detected, and this is perhaps reflected in the analytical figures (Found : C, 73·8; H, 9·0; N, 16·9. Calc. for C_5H_7N : C, 74·1; H, 8·6; N, 17·2%).

1-Methylallyl Cyanide.—By the above procedure, ethyl 1-methylallylmalonate (82 g.) was converted to 1-oximino-2-methylpen-3-enoic acid, which, without isolation, was dehydrated to 1-methylallyl cyanide. Again, evidence of hydrogen cyanide evolution was observed during the fractionation of the nitrile (20·1 g.), which had b. p. 124·0—124·1°/760 mm., n_D^{20} 1·4058 (Found : N, 16·9%).

British Rubber Producers' Research Association,
Tewin Road, Welwyn Garden City, Herts.

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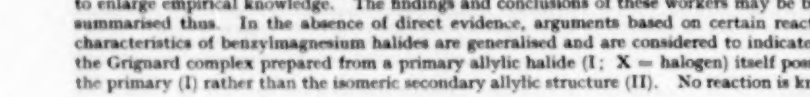
188. *Some Reactions of Geranylmagnesium Chloride.*

By D. Barnard and L. Bateman.

The predominantly primary allylic halide, geranyl chloride (V; X = Cl), is converted by the action of carbon dioxide or ethyl chloroformate on its Grignard derivative into the tertiary allylic acid (VI; X = CO_2H). The main by-product of these reactions is a hydrocarbon mixture derived from the combination of two geranyl fragments. This mixture, which is obtainable in better yield by direct methods, contains a higher proportion of *digeranyl* (VIII) relative to *isodigeranyl* (VII) than found in the corresponding product from related systems. The significance of this finding to the mechanism of the coupling process is discussed.

Little progress has been made in understanding the anomalous behaviour of allylic type Grignard reagents, but the recent extensive study of the butenyl derivatives by Young and his associates (reported in a series of papers, *J. Amer. Chem. Soc.*, 1936—1946) has done much to enlarge empirical knowledge. The findings and conclusions of these workers may be briefly summarised thus. In the absence of direct evidence, arguments based on certain reactivity characteristics of benzylmagnesium halides are generalised and are considered to indicate that the Grignard complex prepared from a primary allylic halide (I; X = halogen) itself possesses the primary (I) rather than the isomeric secondary allylic structure (II). No reaction is known,



however, whereby replacement of the magnesium halide component yields a substantially pure crotonyl derivative (I). On treatment with water or oxygen, mixtures of isomeric butenes or butenols are obtained, respectively, and coupling reactions likewise give heterogeneous products. On the other hand, reactions with carbonyl compounds lead almost exclusively to the Δ^1-olefinic derivatives (IV), the initial interaction of the two reagents being postulated as (III; R_2CO representing an aldehyde, a ketone, or carbon dioxide). This somewhat unusual behaviour may not only introduce complications in synthetic work, but also lead to erroneous conclusions concerning the structure of allylic halides deduced from such reactions (cf. Bateman, Cunneen and Koch, *Nature*, **1949**, **164**, 242; following paper). Lack of diagnostic value is accentuated by the observation (Roberts and Young, *J. Amer. Chem. Soc.*, **1945**, **67**, 148) that

carboxylation of the Grignard compound prepared from 1-methylallyl chloride (II; X = Cl) gives the same acid (II; X = CO_2H) as is obtained by submitting the crotyl halide (I; X = Br) to the same procedure.

For reasons arising out of the difficulty experienced in preparing homogeranic acid (V; X = CO_2H) by standard methods (see the preceding paper), we investigated transformations of the

$CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2X$ (V.) $\qquad$ $CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMeX{\cdot}CH{:}CH_2$ (VI.)

Grignard derivatives of geranyl chloride (V and VI; X = Cl; containing *ca.* 80% of V, as usually isolated, cf. preceding paper). By infra-red spectroscopy (Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915), structural changes analogous to those observed in the butenyl series were readily followed.

Carboxylation of the Grignard complex gave in 30% yield an acid of appreciably lower boiling point and refractive index than homogeranic acid (V; X = CO_2H). Strong infra-red absorption at 908 and 990 cm.$^{-1}$, in agreement with ozonolysis data, identifies the acid as *iso*homogeranic acid (VI; X = CO_2H). *iso*Homogeranamide (VI; X = $CO{\cdot}NH_2$), prepared *via* the *acid chloride* (VI; X = COCl), differed from its isomer (V; X = $CO{\cdot}NH_2$) (*J.*, 1950, 915) in being a non-crystallisable oil (as is the *p*-bromophenacyl ester), but the rather difficultly crystallisable *anilide*, m. p. 49—50°, may be used for characterisation. Similarly, the addition of the Grignard complex in ether to an ethereal solution of ethyl chloroformate at −10° produced an ester which was not easily purified but which on hydrolysis also yielded *iso*homogeranic acid. Insofar as the isolation and physical examination of the products permitted, no evidence of the formation of the isomeric homogeranic acid in these reactions was obtained. These results show (i) that allylic rearrangement from the primary to the tertiary structure occurs with a facility comparable to that of the corresponding primary–secondary change in similar reactions, and (ii) that chloroformic ester is a reagent of non-carbonyl function which adds at the γ-carbon atom of the allylic system.

The principal by-product from both the *iso*homogeranic acid preparations was a high-boiling hydrocarbon mixture, separable by efficient fractionation into components boiling at 171·3—171·9°/12 mm. and 178·9—179·2°/11 mm., respectively, which were present in the proportion of *ca.* 2 : 1. No crystalline derivatives of either could be prepared, but analyses, infra-red

$CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2$ / $CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH_2$ (VII.) $\qquad$ $CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_3$ / $CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_3$ (VIII.)

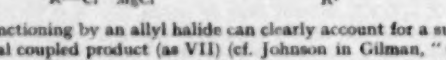
spectra, and ozonolyses establish beyond doubt that the lower- and higher-boiling fractions are respectively iso*digeranyl* (VII) and *digeranyl* (VIII). Ozonolysis of the latter gave succinic acid (92%), but no formaldehyde; the former gave a crystalline acid which analysis indicates to be 2-methylbutane-1 : 2 : 4-tricarboxylic acid and which is clearly the product of oxidative scission at the 7-, 12-, and 1′-double bonds. Consistently, the latter olefin exhibited no marked infra-red absorption at 908 and 990 cm.$^{-1}$ characteristic of the presence of $CHR{:}CH_2$ groups, whereas the former did so with an intensity which virtually establishes its identity as (VII) rather than the related isomer (IX) on this evidence alone.

$CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2$ / $CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_3$ (IX.) $\qquad$ $-CH_2{\cdot}CMe{:}CH{\cdot}CH{\cdot}CH_2{\cdot}CMe(O_2H){\cdot}CH-$ (X.)

Hydrocarbon mixtures of similar composition were subsequently prepared in yields of the order of 70% by coupling geranylmagnesium chloride over silver bromide and by treating geranyl chloride directly over magnesium; (IX) was not detected. Digeranyl is the lower homologue of the naturally occuring triterpene, squalene, and has proved to be a valuable low-molecular model for studying polyisoprene reactivity. The departure from regular head-to-tail isoprene union throughout the molecule is of minor consequence in this connection. For example its oxidation characteristics closely simulate those exhibited by the long-chain polyisoprenes, gutta-percha and natural rubber hydrocarbons, both kinetically (unpublished work by Bolland and by Bateman, Bolland, and Gee) and in the unusual nature of the peroxide unit (X) in the primary product (Bolland and Hughes, this vol., p. 492; and unpublished).

The formation of the relatively high proportion of (VIII) to (VII) compared with the proportions of the related isomers derived from crotonyl and cinnamyl halides—where the

forms corresponding to (VII) predominate to the extent of about 9 : 1 and 4 : 1 respectively—is an interesting feature bearing on the mechanism of the coupling process. Koch (*J.*, **1948**, 1111) recently commented on the differences found in the crotonyl and the cinnamyl systems and has suggested that the factor responsible is increased resonance stabilisation of the 3-phenylallyl as compared with the 3-methylallyl grouping. The present finding with a system intermediate in such electronic character between the above groups obviously renders any simple explanation in these terms inadequate. If we assume with Young and Roberts (*J. Amer. Chem. Soc.*, **1946**, **68**, 1472) that the Grignard complex possesses an essentially covalent primary allylic structure,* the structural course of the reaction with a simple alkyl halide (*J.*, **1950**, **941**), just as with ethyl chloroformate and with chloromethyl *n*-butyl ether (Young, Roberts, and Wax, *J. Amer. Chem. Soc.*, **1945**, **67**, 841), requires that a " chelated " transition complex similar to that envisaged for carbonyl-compound interaction (Johnson, *J. Amer. Chem. Soc.*, **1933**, **55**, 3029; Young and Roberts, *loc. cit.*) promotes combination thus :†



Analogous functioning by an allyl halide can clearly account for a substantial proportion of the unsymmetrical coupled product (as VII) (cf. Johnson in Gilman, " Organic Chemistry," Wiley and Sons, New York, 2nd edn., **1943**, p. 1881). However, several independent phenomena—*e.g.*, electro-chemical behaviour indicative of an ionised salt-like structure (Evans and Pearson, *J. Amer. Chem. Soc.*, **1942**, **64**, 2865), or the profound influence of extraneous metallic compounds, notably cobaltous chloride, on the course of Grignard reactions, probably caused by initiation of free-radical processes (Kharasch *et al.*; for a summary see *Ann. Reports*, **1944**, **195**; cf., however, Wilds and McCormack, *J. Org. Chem.*, **1949**, **1**, 45), and the small variations in reaction conditions and in the structure of the addenda which determine whether benzylmagnesium halides yield normal or abnormal (*o*-tolyl) products (Austin and Johnson, *ibid.*, **1932**, **54**, 647)—clearly signify that Grignard reagents possess diverse reactivity potentialities which are not distinctly separated energetically. Hence, the liberation of allylic free radicals or anions, and their participation in reactions occurring concurrently with the " chelation " process are to be expected. Any tendency exhibited in this respect by the 3-methylallyl system will be enhanced in the 3-phenylallyl and 3 : 3-dialkylallyl systems owing to the increased facility for radical or ionic dissociation afforded by the greater resonance energies of the hydrocarbon fragments thus produced. Since processes involving free allylic ions (see, *e.g.*, Catchpole, Hughes, and Ingold, *J.*, **1948**, 8; Campbell and Young, *J. Amer. Chem. Soc.*, **1947**, **69**, 688, 3066) or radicals (Bolland and Koch, *J.*, **1945**, 445; cf. *J.*, **1950**, 941) invariably lead to mixtures of isomeric products, the increased heterogeneity of the hydrocarbon dimers derived from cinnamyl and geranyl halides is understandable. In comparing the last two systems among themselves, however, account must be taken of an important difference in location of the reactivity focus in the respective hydrocarbon radicals or ions. In contrast to the situation prevailing in covalent compounds—where the primary allylic isomer ($CHR{:}CH{\cdot}CH_2X$) is much the more favoured thermodynamically—experiment shows (Birch, *Faraday Soc. Discussion*, **1947**, **2**, 246, where other references are given), and theory readily interprets (de la Mare, Hughes, and Ingold, *J.*, **1948**, 17), that the charge in a 3-arylallyl anion is sited predominantly at $C_{(\gamma)}$ ($Ar{\cdot}\bar{C}H{\cdot}C{:}CH_2$), whereas in a 3-alkylallyl anion it is at $C_{(\alpha)}$ ($Alk{\cdot}(CH_2{:}CH{\cdot}\bar{C}H_2)$. Accepting that $C_{(\gamma)}{-}C_{(\gamma)}$ combination is repressed by special factors which cannot now be discussed, it is clear that this distinction—which undoubtedly exists equally in the free-radical analogues—is in accord with the experimental observations concerning the variations in $C_{(\alpha)}{-}C_{(\alpha)}$ and $C_{(\gamma)}{-}C_{(\alpha)}$ coupling in the geranyl and cinnamyl systems.

* Two arguments additional to those advanced by Young and Roberts in support of this assumption warrant consideration. First, reactions of carbonyl compounds with the sodium derivative of allylbenzene in liquid ammonia, *i.e.*, conditions where carbanions certainly participate in the reaction, yield isomeric product mixtures (Campbell and Young, *J. Amer. Chem. Soc.*, **1944**, **66**, 3066), in contrast to the remarkably homogeneous secondary allylic products obtained from the corresponding Grignard reactions. Secondly, the formation of structurally analogous carbinols and acids from crotonyl- and cinnamyl-magnesium halides (Gilman and Harris, *J. Amer. Chem. Soc.*, **1931**, **53**, 3541) suggests strongly that these two Grignard reagents possess a common basic structure. For reasons outlined later in this paper, covalent attachment of the MgX group to the hydrocarbon component must be inferred, since in dissociated or pseudo-dissociated formulations the location of the principal reactivity centre at different points in the two hydrocarbon units should be reflected in dissimilarities of the product.

† An interpretation of the factors directing R- to the γ- rather than to the α-carbon atoms is given later (*J.*, **1950**, **941**).

Experimental.

Geranyl Chloride.—The commonly isolated isomeric mixture (cf. preceding paper) containing approx. 80% of the primary geranyl chloride (V; X = Cl) and 20% of the tertiary linalyl chloride (VI; X = Cl) has been used in the present work.

Geranylmagnesium Chloride.—The reaction leading to this Grignard reagent is difficult to start and can be markedly inefficient. The following was found to be the most satisfactory procedure. Magnesium turnings (12·5 g.) were covered with anhydrous ether (500 ml.), and 9 g. of geranyl chloride and a crystal of iodine added. A 15% solution of geranyl chloride in ether (3 ml.), vigorously reacting with a small amount of magnesium previously activated by heating with iodine, was added; on gently warming, the main reaction then started. More ether (500 ml.) was added immediately, and geranyl chloride (79 g.) dropped in at a rate sufficient to keep the mixture warm but not refluxing (2—4 hours). An atmosphere of dry nitrogen was maintained in the apparatus throughout these operations. Even in such conditions, much of the geranyl chloride participates in coupling reactions, as shown by the turbidity of the reaction mixture and by the use of less than the theoretical amount of magnesium.

iso*Homogeranic Acid.*—A rapid stream of dry carbon dioxide was passed for 2 hours into an ethereal solution of geranylmagnesium chloride, prepared as described above and maintained at −30°. The resulting mixture was cautiously treated with ice-cold 25% sulphuric acid (150 ml.), and the ethereal layer separated and extracted with 2*N*-sodium hydroxide. iso*Homogeranic* (3 : 7-*dimethylocta*-1 : 6-*diene*-3-*carboxylic*) *acid* (25·5 g.), thus extracted was isolated in the usual way and had b. p. 99—100°/0·05 mm., n_D^{20} 1·4665 (Found: C, 72·6; H, 10·0%; equiv., 182·4. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%; equiv., 182·0).

iso*Homogeranamide.*—Thionyl chloride (3·5 ml.) was added slowly with stirring to *iso*homogeranic acid (5·8 g.) in ether (10 ml.) and pyridine (2·6 g.). The mixture was finally refluxed for 30 minutes, then cooled, diluted with ether (30 ml.), and filtered. Fractionation of the filtrate gave the *chloride* (5 g.) as a colourless oil, b. p. 49—51°/0·1 mm., n_D^{20} 1·4754. This was added dropwise with stirring to ethanol (35 ml.) cooled to 0° and saturated with dry ammonia. After evaporation of the solvent under reduced pressure, the residue was extracted with ether. Fractionation of the extracts yielded iso*homogeranamide* as an oil (4·4 g.), b. p. 103—105°/0·05 mm., n_D^{20} 1·4920 (Found: C, 72·9; H, 10·7; N, 7·9. $C_{11}H_{19}ON$ requires C, 72·9; H, 10·6; N, 7·8%). The infra-red spectrum of this amide exhibits strong bands at 916 and 1000 cm.$^{-1}$ indicative of the $CHR:CH_2$ grouping.

iso*Homogerananilide.*—*iso*Homogeranoyl chloride (2·6 g.) was added slowly to an ice-cold solution of re-distilled aniline (1·84 g.) in ether (5 ml.). After further dilution with ether (20 ml.), the filtered solution was washed with dilute hydrochloric acid, sodium hydroxide solution, and water, dried (K_2CO_3), and freed from solvent. The residual oil crystallised slowly on storage at 0°. Fractional elution from alumina using light petroleum (b. p. 40—60°), followed by sublimation at 0·05 mm., yielded the pure *anilide*, m. p. 50·5—51° (Found: C, 79·2; H, 8·7; N, 5·7. $C_{17}H_{25}ON$ requires C, 79·3; H, 9·0; N, 5·5%).

Ozonolysis of iso*Homogeranic Acid.*—The acid (1·2 g.) in glacial acetic acid (12 ml.) was treated with a slow stream of ozonised oxygen for 3 hours at room temperature. The resulting solution was dropped slowly into boiling water (100 ml.) containing suspended zinc dust (7 g.), and the volatile distillate passed into a solution of dimedon (2 g.) in aqueous ethanol. The formaldehyde–dimedon compound separated (0·30 g.), m. p. 187—188°, mixed m. p. with an authentic specimen, 188—188·5°.

Reaction of Ethyl Chloroformate with Geranylmagnesium Chloride.—The Grignard reagent prepared from geranyl chloride (106 g.) in ether (1250 ml.) was added slowly with stirring to freshly distilled ethyl chloroformate (67 g.) in ether (250 ml.) at −10°. After the addition was complete, the mixture was kept for 1 hour at room temperature and then acidified (dilute sulphuric acid), and the product in the ethereal layer recovered in the usual way. On distillation, two main fractions were collected: b. p. 100—114°/12 mm. (25 g.), and b. p. 108—118°/0·05 mm. (30 g.). The former was hydrolysed by refluxing it with potassium hydroxide (10 g.) in ethanol (200 ml.) for 4 hours. Pure *iso*homogeranic acid, b. p. 89—90°/0·01 mm., n_D^{20} 1·4669 (15 g.) was obtained. The derived chloride and amide were identical with the corresponding compounds prepared as described previously.

By-products from the Above Reactions of Geranylmagnesium Chloride.—In all the above Grignard reactions, a considerable amount of a high-boiling hydrocarbon by-product was produced, having b. p. 134—139°/0·5 mm., n_D^{20} 1·4820—1·4838. Analytical data indicated that the *substance* originated in the coupling of two molecules of the Grignard reagent (Found, lower-boiling fraction: C, 87·5; H, 12·4%; *M*, 276. Higher-boiling fraction: C, 87·6; H, 12·4%; *M*, 280. $C_{20}H_{34}$ requires C, 87·5; H, 12·5%; *M*, 274).

Coupling Reaction of Geranylmagnesium Chloride in the Presence of Silver Bromide.—Finely ground and vacuum-dried silver bromide (155 g.) was added slowly to a vigorously stirred Grignard solution prepared from geranyl chloride (170 g.) and magnesium (24 g.) in ether (600 ml.) and maintained at 0°. Reaction was made evident by the formation of metallic silver, and completed by refluxing the mixture for 1 hour. After cooling and acidification with dilute sulphuric acid, the ethereal layer was separated and worked up in the usual way. A small portion of the product was freed from volatile material by being kept at 10^{-4} mm. in contact with a trap cooled in liquid air, and then distilled at 40°/10^{-6} mm. in a pot-type molecular still, and then had n_D^{20} 1·4828. This sample showed no change in infra-red spectrum and had almost the same *n* (1·4832) after being heated at 175° in a vacuum for 135 minutes, thus proving the absence of isomerisation [*e.g.*, from (IX) to (VIII)] under normal fractionation conditions which might mask the true composition of the coupled product. The bulk of the material was distilled from sodium (b. p. 132—137°/0·5 mm.; 102 g.), and then carefully fractionated through a Fenske-type column packed with glass helices (11 theoretical plates); later fractionations were carried out using a column packed with gauze rings (22 theoretical plates) with similar results. Separation into two homogeneous fractions was achieved with very little fore-run and residue; an intermediate mixture of the two fractions provided the major loss.

iso*Digeranyl* (50 g.) (2 : 6 : 9 : 13-*tetramethyl*-9-*vinyltetradeca*-2 : 6 : 12-*triene*) had b. p. 171·3—171·9°/12 mm., n_D^{20} 1·4821 (Found: C, 87·6; H, 10·6%; *M*, 277. $C_{20}H_{34}$ requires C, 87·5; H, 12·5%;

M, 274). The infra-red spectrum reveals the presence of the unsaturated grouping $CH_2{:}CHR$ in addition to the grouping $CHR{:}CR_2$ (see preceding paper). *Ozonolysis.* A slow stream of ozonised oxygen was bubbled through a solution of the hydrocarbon (2 g.) in carbon tetrachloride (20 ml.) at −15° for 4 hours. Removal of the solvent left a semi-crystalline ozonide, which was dissolved in aqueous (50%) acetic acid (20 ml.), 30% hydrogen peroxide was added (10 ml.), and the solution boiled under reflux for 1·5 hours. After the solution had been made alkaline and extracted with ether, the re-acidified solution was extracted with ether to yield an oil which was dissolved in the minimum quantity of light petroleum (b. p. 60—80°) and kept at −5° for several days. Lustrous sheaves of crystals, which separated in small yield, had m. p. 126—127° after high-vacuum sublimation and recrystallisation from light petroleum (Found: C, 47·3; H, 6·1. $C_8H_{12}O_4$ requires C, 47·1; H, 5·9%).

Digeranyl (2 : 6 : 11 : 15-*tetramethylhexadeca*-2 : 6 : 10 : 14-*tetraene*) (24 g.) had b. p. 178·9—179·2°/11 m., n_D^{20} 1·4837 (Found: C, 87·3; H, 12·5%; *M*, 277; $\equiv$, 4·05 by microhydrogenation. $C_{32}H_{54}$ requires C, 87·5; H, 12·5%; *M*, 274; $\equiv$, 4·00). The infra-red spectrum shows the olefinic unsaturation to be solely of the type $CHR{:}CR_2$ (see preceding paper). *Ozonolysis.* (i) Ozonised oxygen was passed slowly through a solution of digeranyl (0·5 g.) in glacial acetic acid (15 ml.) for 3 hours. The resulting solution was dropped into boiling water (100 ml.) containing zinc dust (7 g.), and the distillate passed into an ice-cold saturated solution of dimedon in aqueous ethanol. No formaldehyde derivative was obtained. (ii) Digeranyl (1·51 g.) in anhydrous carbon tetrachloride (30 ml.) was ozonised at −20° for 4·5 hours. After decomposition of the ozonide in boiling aqueous acetic acid containing hydrogen peroxide as described above and destruction of excess of peroxide by the addition of silver oxide, the solution was freed from soluble or colloidal silver compound with dilute hydrochloric acid, filtered, and concentrated under reduced pressure to *ca.* 2 ml. The succinic acid which separated was sublimed at 0·1 mm. and had m. p. and mixed m. p. 184—185° (Found: C, 41·0; H, 5·2%; equiv., 60. Calc. for $C_4H_6O_4$: C, 40·6; H, 5·1%; equiv., 59). Yield, 0·595 g. (91·5% theoretical).

Coupling Reaction of Geranyl Chloride over Magnesium.—Geranyl chloride (210 g.) was converted into the Grignard reagent in the usual manner, using, however, only half the theoretical quantity of magnesium. The product on isolation consisted largely of the digeranyl hydrocarbons (101 g.). Fractionation yielded pure digeranyl (27 g.) and *iso*digeranyl (52 g.).

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British Rubber Producers' Research Association,
Tewin Road, Welwyn Garden City, Herts.

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189. *The Reaction of Hexa-1 : 5-diene with N-Bromosuccinimide.*

By L. Bateman, J. I. Cunneen, Joyce M. Fabian, and H. P. Koch.

By analytical application, qualitative and approximately quantitative, of infra-red spectroscopy, and by conversion into known derivatives by reactions along well established structural routes, it has been demonstrated, contrary to the conclusions of Karrer and Schneider (*Helv. Chim. Acta*, 1948, **31**, 395), that the monobromide isolated from the reaction named in the title consists mainly of 1-bromohexa-2 : 5-diene, mixed with about 10% of the 3-bromo-$\Delta^{1,5}$-isomer.

During an investigation of certain allylic terpenoid bromides it became of interest to attempt the preparation of the bromide (I; X = Br) and to see whether dehydrobromination yielded hexa-1 : 3 : 5-triene. In view of the investigations of Winstein and Young (*J. Amer. Chem. Soc.*, 1936, **58**, 104), of Kharasch, Margolis, and Mayo (*J. Org. Chem.*, 1936, **1**, 393), and of Young, Richards, and Azorlosa (*J. Amer. Chem. Soc.*, 1939, **61**, 3070) into the isolation and interconversion of related allylic bromides, it was apparent from the outset that this bromide would generally co-exist with its allylic isomer (II; X = Br) and that its preparation substantially pure would present much difficulty. It was, therefore, surprising that Karrer and Ringli (*Helv. Chim. Acta*, 1947, **30**, 863) reported the preparation of (I; X = Br) by treatment of hexa-1 : 5-diene (diallyl) with *N*-bromosuccinimide in boiling carbon tetrachloride. Further bromination by the same method yielded a crystalline dibromide formulated as (III). A

(I.) $CH_2{:}CH{\cdot}CH_2{\cdot}CHX{\cdot}CH{:}CH_2$ $CH_2{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2X$ (II.)

(III.) $CH_2{:}CH{\cdot}CHBr{\cdot}CHBr{\cdot}CH{:}CH_2$ $XCH_2{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2Y$ (IV.)

second, correcting paper (*idem, ibid.*, 1947, **30**, 1771) reported the dibromide to be the conjugated compound (IV; X = Y = Br) (Farmer, Larria, Switz, and Thorpe, *J.*, 1927, 2937), and doubt was expressed concerning the correctness of the structure assigned to the monobromide. This doubt was quickly resolved in favour of the original assignment by Karrer and Schneider (*ibid.*, 1948, **31**, 395), who condensed the monobromide with acetophenone in the presence of magnesium and ether, ozonised the resulting *tert.*-alcohol, and measured the liberation of 1·44 g.-mols. of

formaldehyde; no acetaldehyde was detected. The last observation was significant since Karrer and Schneider had found that mild hydrolysis of the acetate obtained from the bromide by silver acetate produced an unsaturated alcohol which yielded *n*-hexanol on catalytic reduction. An ω-bromide structure therefore became a possibility and consideration was mainly given to (IV; X = H; Y = Br) rather than to (II; X = Br), presumably because of analogy with the dibromide structure. However, the ozonolysis apparently serves to eliminate this possibility, and requires that the formation of the primary alcohol be attributed to rearrangement occurring during its synthesis from the bromide.

The identification of diallyl monobromide * as (I; X = Br) is so contrary to expectation based on the behaviour of similar bromides (Young *et al.*, *loc. cit.*) as to provoke critical examination of the supporting evidence. Three unsatisfactory features are then evident. First, the absence of any mention of interconversion (I; X = Br) $\rightleftharpoons$ (II; X = Br) suggests that Karrer and Schneider overlooked the controlling influence on the composition of the product likely to be exerted by this ready isomerisation. Secondly, it seems that no isomerisation occurs during the monobromination stage and yet two double-bond displacements and the migration of the initially substituted bromine atom occur on further reaction. Thirdly, the presumed diagnostic criterion afforded by ozonolysis is almost certainly valueless since, in the case of the closely similar 1-methylallyl and 3-methylallyl bromides, Roberts and Young (*J. Amer. Chem. Soc.*, 1945, **67**, 148, 319; 1946, **68**, 1472) established that, irrespective of the isomeric nature of the original halide, reaction of the derived Grignard complex with carbonyl compounds yields almost pure secondary allylic derivatives.

The ever-present possibility of allylic isomerisation accompanying reaction militates severely against the successful application of purely chemical methods to solve this structural problem.† Accordingly, our investigations (which date from the appearance of Karrer and Ringli's first paper) have sought to make full use of infra-red and ultra-violet spectroscopy (cf. especially Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915).

The Composition of Diallyl Monobromide.—We find that analytically pure diallyl monobromide boiling over the temperature range reported by Karrer and Ringli and prepared either according to these authors' directions or by the modified procedures referred to later is neither (I; X = Br) nor (IV; X = H; Y = Br) but is *essentially* (II; X = Br). Its infra-red absorption spectrum exhibits a strong band at 965 cm.$^{-1}$, characteristic of the presence of the CHR:CHR grouping and absent in diallyl, as well as bands at 918 and 990 cm.$^{-1}$ caused by CH_2:CHR groups. The intensity of the latter band is approximately half that of the same absorption in diallyl. The ultra-violet absorption spectrum confirms the absence of diene conjugation.

With carbon dioxide the Grignard complex derived from the bromide yields the secondary allylic *hexa-1 : 5-diene-3-carboxylic acid* (I; X = CO_2H) (*p-bromophenacyl* ester, m. p. 32—33°), whose infra-red absorption differs markedly from the bromide but closely resembles that of the parent olefin between 900 and 1000 cm.$^{-1}$. This practically quantitative change from primary allylic type has been incontrovertibly demonstrated by Young and Roberts (*loc. cit.*) to be a general characteristic of carbonyl compound–butenylmagnesium halide reactions, and therefore we can confidently assert that while Karrer and Schneider's structure for the bromide is wrong their formulation of the *tert.*-alcohol prepared from acetophenone as (I; X = $^-$CPhMe·OH) is right. When the bromide is converted into an ether by a hot concentrated solution of sodium ethoxide in ethyl alcohol, the product exhibits intense ultra-violet absorption at 2250 A., indicative of its conjugated nature and, in conformity, its infra-red absorption spectrum reveals the presence and absence of CH:CH and CH_2:CH_2 groups, respectively. The ether must therefore be either *1-ethoxyhexa-2 : 4-diene* (IV; X = H; Y = OEt) or the 3-ethoxy-isomer. The location of the ultra-violet absorption maximum affords strong evidence favouring the former. This indication has been verified completely by catalytic reduction and identification of the product as *n*-hexyl ethyl ether by cleavage with hydriodic acid and conversion into *n*-hexyl*iso*thiuronium picrate, m. p. 156°. Since it is now well authenticated that bimolecular (S_N2) replacement reactions of allylic halides with ethoxyl ions lead wholly to attachment of the entrant group at the site of the displaced group (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 627; Catchpole and Hughes, *J.*, 1948, 4; Roberts, Young, and Winstein, *J. Amer. Chem. Soc.*, 1942, **64**, 2157; Young and

* Throughout this paper, "diallyl monobromide" designates the isolated *substitution* product irrespective of its isomeric constitution.

† It should be noted that ozonolysis of allylic compounds possessing α-methylenic functional groups can provide particularly untrustworthy information (Young, McKinnis, Webb, and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 293).

Andrews, *ibid.*, 1944, **66**, 421), combination of the ethoxyl group at a terminal carbon atom under the drastic S_N2 conditions employed provides independent and specific information concerning the location of the original bromine atom. The double-bond shift accompanying alcoholysis exemplifies the well-known lability of 1 : 4-dienes to such isomerisation under proton-transfer conditions. We have not repeated Karrer and Ringli's bromide ⟶ acetate ⟶ alcohol sequence since the tendency to S_N1 replacement (and therefore to isomeric mixtures) in the first stage (see, *e.g.*, Catchpole, Hughes, and Ingold, *J.*, 1948, 8) introduces ambiguity into any structural deductions. The procedure employed for isolation by the Swiss workers would hardly be likely to determine whether the alcohol said to be (IV; X = H; Y = OH) was free from (I; X = OH), and the mild hydrolytic conditions used in the second stage suggest that (II; X = OH) may also have been present.

No uncertainty attaches to the data and conclusions so far presented, but the normal existence of similar allylic bromides as isomeric mixtures containing *ca.* 15% of the secondary allylic form (Young *et al.*, *loc. cit.*), together with the fact that the bromination conditions and the subsequent isolation of the product both strongly facilitate interconversion (cf. following paper), indicate that the possibility of isolating a homogeneous diallyl monobromide as the reaction product is negligible. An immediate and affirmative indication of isomeric heterogeneity is afforded by the observation that analytically pure monobromide boils over a range of about five degrees (cf. Karrer and Ringli, *loc. cit.*). More significantly, the infra-red spectra of head and of tail fractions showed small but readily detectable variations corresponding to a higher concentration of the secondary allylic isomer (I; X = Br) in the lower-boiling material. In agreement with the work of Young *et al.* (*loc. cit.*), this partial isomeric separation on distillation was also reflected in substantial differences in refractive index. The difficult and tedious problem of accurate isomeric analysis, necessitating the separate physical characterisation of both components, is beyond the scope of the present work, but an approximate estimation can be deduced by comparing the absolute extinction coefficients of the infra-red absorption frequencies due to the CHR:CHR and CH_2:CHR groups in the bulked monobromide product. Such analysis (see the Experimental section) is complicated by the occurrence of *cis*- and *trans*-forms of the 1-bromo-Δ^4-isomer, but it is estimated that 5—15% of (I; X = Br) is present in a typical monobromide preparation.

Secondary Products of Reaction.—As reported by Karrer and Ringli (*loc. cit.*), a minor product of the diallyl-*N*-bromosuccinimide reaction is the crystalline, conjugated dibromide (IV; X = Y = Br), which is better prepared by further bromination of the monobromide and displays spectroscopic characteristics in full accord with its established molecular structure. We have also isolated a second dibromide—a liquid in which the elements of hydrogen bromide have added to the CH:CH centre of the monobromide. This compound has not been specially investigated, but its spectral properties together with knowledge of the orientation of hydrogen bromide addition to allyl bromide under similar conditions suggest fairly definitely that it is **4 : 6-*dibromohex*-1-*ene***. Small quantities of hydrogen bromide are often evolved during bromination with *N*-bromosuccinimide; larger quantities are to be expected only when spontaneous dehydrobromination is occurring simultaneously (see, *e.g.*, Dorée, McGhie, and Kurzer, *J.*, 1949, 570). Under the conditions of reaction, the bromide (II; X = Br) shows little tendency to liberate hydrogen bromide (*e.g.*, during further bromination), as might be expected from its structure, but the isomer (I; X = Br) may well do so very readily, and in doing so may provide the source of the polymeric tar which is formed in considerable quantity. Kharasch, Nudenberg, and Sternfield (*J. Amer. Chem. Soc.*, 1940, **62**, 2032) have actually stated that a tendency to just this behaviour is exhibited by the corresponding chloride even at room temperature. Adequate quantities of (I; X = Br) are likely to be available for dehydrobromination on the scale required, for there is reason to believe (following paper) that (I; X = Br) and (II; X = Br) are formed in somewhat comparable amounts in the primary bromination process, although the former cannot survive isolation in amounts greater than its thermodynamic equilibrium proportion.

The Reactivity of Diallyl towards N-Bromosuccinimide.—Bromination proceeds far less readily with diallyl than with the singly unsaturated Δ^1-olefin, oct-1-ene (following paper), and the isoprenic diene, 2 : 6-dimethylocta-2 : 6-diene (unpublished). Our experience is that the use of the olefin in excess rather than in equimolecular porportion to the brominating agent (cf. Karrer and Ringli, *loc. cit.*) expedites reaction and lessens contamination of the monobromide with by-products. However, under conditions such that reaction with the last two olefins is complete within 15 minutes, reaction with diallyl is incomplete after two hours. Irradiation with ultra-violet light produces a small acceleration, but this is offset by an increase in secondary

decomposition, shown by a marked darkening of the reaction mixture. If one accepts as a reasonable assumption, in the absence of positive evidence, that a rate-determining step in the bromination is the detachment of an α-methylene hydrogen atom (Bloomfield, *J.*, 1944, 114; cf. following paper), then the enhanced reactivity of 2 : 6-dimethylocta-2 : 6-diene compared with diallyl can readily be associated with the increased mesomerism of the methylallyl as compared with the allyl radical. The rate difference between oct-1-ene and diallyl is much less obvious, especially as Bolland (*Trans. Faraday Soc.*, in the press) has found that peroxide radicals abstract α-methylene hydrogen atoms from both molecules with practically the same efficiency—a result which should be general for any similar hydrogen exchange.

Added in proof. On the basis of ozonolysis results, Karrer and Perl (*Helv. Chim. Acta*, 1950, **33**, 36) have rejected our conclusions as presented in a preliminary note (*Nature*, 1949, **164**, 242), and identify the isolated monobromide as essentially $CHMe{:}CH{\cdot}CHBr{\cdot}CH{:}CH_2$ (V). The analytical data supporting this view are, however, inherently uncertain (cf. *J.*, 1950, 915), and it is opposed by the diverse and fully consistent evidence reported in this and the following paper, and the facts that it involves unusual prototropic changes [*e.g.*, the conversion of (V) into (I; X = CO_2H) during an ordinary Grignard reaction], and that 3-bromo-1 : 4-dienes do not normally exist because the lability of the bromine atom allows full rein to the conjugative tendency of the 1 : 4-diene unit [*e.g.*, attempted preparations of 1-phenylallyl bromide and linaloyl bromide always yield the isomeric cinnamyl and geranyl compounds, respectively, and diallyl dibromide is obtained as (IV; X = Y = Br) for the same reason].

Experimental.

Hexa-1 : 5-diene, prepared from allyl bromide (Cortese, *J. Amer. Chem. Soc.*, 1929, **51**, 2267), had b. p. 59·6°/758 mm. Its infra-red spectrum reflects unambiguously the absence of any but $CH_2{:}CHR$-type unsaturation (cf. Barnard *et al.*, *loc. cit.*).

Purchased and synthesised batches of *N*-bromosuccinimide varied greatly in efficacy. Recrystallisation from water was found to yield consistently active material.

Reaction of Hexa-1 : 5-*diene with* N-*Bromosuccinimide.*—(*a*) *Karrer and Ringli's conditions.* The olefin (50·5 g., 0·62 mole), *N*-bromosuccinimide (89 g., 0·5 mole), carbon tetrachloride (300 ml.), and benzyl peroxide (0·2 g.*) were refluxed for 8 hours. Removal of the insoluble succinimide and the solvent, and distillation of the liquid residue gave the following fractions of 1-*bromohexa*-2 : 5-*diene* admixed with a little 3-bromohexa-1 : 5-diene: (1) 1 g., b. p. 39—40°/11 mm., n_D^{15} 1·4963 (Found: C, 44·2; H, 5·7; Br, 50·2. C_6H_9Br requires C, 44·7; H, 5·6; Br, 49·7%); (2) 2·1 g., b. p. 40—41°/11 mm., n_D^{15} 1·4985; and (3) 9·5 g., b. p. 41—44°/11 mm., n_D^{15} 1·5005 (Found: C, 44·5; H, 5·7; Br, 50·1%).

(*b*) *Large excess of olefin.* The olefin (131 g., 1·6 moles), *N*-bromosuccinimide (100 g., 0·56 mole), carbon tetrachloride (230 ml.), and benzoyl peroxide (0·2 g.) were refluxed for 4 hours. Fractionation of the product gave (1) 2·9 g., b. p. 39—40°/10 mm., n_D^{15} 1·4970 (Found: C, 44·5; H, 5·7; Br, 50·0%), (2) 11 g., b. p. 40—41·5°/10 mm., n_D^{15} 1·4996, and (3) 12·3 g., b. p. 41·5—44°/11 mm., n_D^{15} 1·5009 (Found: C, 44·4; H, 5·7; Br, 49·7%).

(*c*) *Irradiation with ultra-violet light.* The olefin (70·5 g., 0·86 mole), *N*-bromosuccinimide (178 g., 1·0 mole), carbon tetrachloride (300 ml.), and benzoyl peroxide (0·2 g.) were irradiated with a Hanovia S. 500 mercury-arc lamp 15 cm. distant and refluxed for 2·5 hours. Two fractions of the distilled product were collected: (1) 4·2 g., b. p. 39—40°/10 mm., n_D^{15} 1·4980 (Found: C, 44·5; H, 5·7; Br, 50·2%), and (2) 13·9 g., b. p. 40—43°/10 mm., n_D^{15} 1·4990 (Found: C, 44·5; H, 5·7; Br, 49·9%).

Ultra-violet Spectrographic Examination of Diallyl Monobromide.—The bulked distillate from (*a*) displayed no selective absorption between 2200 and 3400 A.

Infra-red Spectrographic Examination of Diallyl Monobromide.—The bulked distillate from (*a*) exhibited strong infra-red absorption at 965, 918, and 990 cm.$^{-1}$. Comparison with diallyl (much stronger absorption at 913 and 990 cm.$^{-1}$, no absorption at 965 cm.$^{-1}$) and allyl bromide (strong absorption at 927 and 990 cm.$^{-1}$, no absorption at 965 cm.$^{-1}$) indicated that the product was essentially (II; X = Br).

For the reason given in the next paragraph, the ratio of the observed molecular extinction coefficient at 965 cm.$^{-1}$ to that exhibited by a pure reference compound does not afford an absolute measure of the concentration of CH:CH units. However, comparison of the relative variations at 918 and 965 cm.$^{-1}$ in the several fractions yields a *relative* measure of the proportion of $CH_2{:}CHR$ and CHR:CHR groups. The following optical densities (determined immediately after isolation of the fractions, using *ca.* 4% solutions in carbon tetrachloride and the same absorption cell throughout) reveal that an increase in b. p. and refractive index reflects an increase in the proportion of the primary allylic isomer (cf. Young, Richards, and Azorlosa, *loc. cit.*):

Bromide fraction.	*a*1.	*b*1.	*c*1.	*c*3.	*a*3.	*b*3.
n_D^{15}	1·4963	1·4970	1·4980	1·4990	1·5003	1·5009
$\log (I_0/I)_{918}/\log (I_0/I)_{965}$	1·90	1·64	1·51	1·08	1·11	1·01

In principle, two independent, absolute estimations of the isomeric composition of the bromide product are obtainable by the comparison of its extinction coefficients (i) at 918 or 990 cm.$^{-1}$ and (ii) at

* On the scale described, Karrer and Ringli would have added 2·08 g. The essential features of the reaction are obviously insensitive to the use of an amount more in keeping with the catalytic rôle of the peroxide.

965 cm.$^{-1}$ with standard values determined from appropriate reference compounds. Since the former dual absorption is common to both isomers whereas the latter absorption is due solely to the presence of the $\Delta^{1,5}$-isomer, the second comparison is potentially the more sensitive. However, absorption at 965 cm.$^{-1}$ originates in the *trans*-form of the CHR:CHR'' grouping only, and hence the occurrence of both *cis*- and *trans*-forms of the latter isomer would obviously vitiate this simple analysis. That this situation actually prevails was evident first from the much lower proportion of the $\Delta^{1,5}$-isomer thus estimated as compared with the proportion derived from method (i), and secondly from the occurrence of absorption at 680 cm.$^{-1}$ attributable to the *cis*-CHR':CHR'' grouping (Kilpatrick and Pitzer, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 191; Sheppard and Sutherland, *Proc. Roy. Soc., A*, 1949, **196**, footnote p. 203). Since a standard value of the extinction coefficient at 965 cm.$^{-1}$ of a *trans*-dialkylethylene is available (Hart and Meyer, *J. Amer. Chem. Soc.*, 1949, **71**, 1980),* comparison at this frequency serves to determine the concentrations of *trans*-1-bromohexa-2 : 5-diene. Technical difficulties, as well as the absence of a satisfactory standard, prohibit a corresponding quantitative determination of the *cis*-form. It is only possible, therefore, to estimate the chemical isomeric composition of the bromide mixture by method (i); as the data collected in the following table show, the results have limited accuracy. Since the

Compound.	Absorbing unit.	Frequency (cm.$^{-1}$).	Molecular extinction coefficient (per absorbing unit).	Composition of diallyl monobromide. 3-Bromohexa-1 : 5-diene (%).	1-Bromohexa-2 : 5-diene (% *trans*-).
Hexa-1 : 5-diene	CH_2:CHR	913	107		
		990	45		
Allyl bromide ...	CH_2:CHR	927	126		
		983	45		
trans-Hex-2-ene ...	*trans*-CHR:CHR	965	157 †	—	—
Bulked sample from preparation (*a*)	CH_2:CHR	918	113	5	—
		990	50	11	—
	trans-CHR:CHR	965	100	—	67

† From Hart and Meyer, *loc. cit.*

absorption at 990 cm.$^{-1}$ appears to be insensitive to substitutional changes in the reference compounds, comparison at this frequency is considered to provide the more reliable estimate, correct to $\pm 5\%$. By difference, *cis*-1-bromohexa-2 : 5-diene must be present to the extent of about 22%.

4 : 6-*Dibromohex*-1-*ene*.—Fractionation of the liquid remaining after fraction 3 from preparation (*a*) had distilled gave : (4) a mixture of increasing bromine content, b. p. 53—86°/14 mm., n_D^{20} 1·5121 (2·6 g.); and (5) a dibromide, b. p. 86—87°/14 mm., n_D^{20} 1·5215 (Found : C, 30·1; H, 4·2. $C_6H_{10}Br_2$ requires C, 29·8; H, 4·1%) (6·3 g.). Infra-red spectroscopic examination of the dibromide established the presence of CH_2:CHR groups and the absence of CHR:CHR groups; this material therefore results from the addition of hydrogen bromide either non-terminally to (II; X = Br) or terminally to (I; X = Br). In the latter case, addition is possible at the double bond nearer to, or further from, the initially substituted bromine atom. No attempt has been made to determine the structure of the product formally, but the following deductions appear to be virtually conclusive. No selective absorption occurs between 2200—3400 A., and the general absorption (*e.g.*, log ε = 3·0 at 2200 A.) is much less than that of the specimen of diallyl monobromide referred to above (*e.g.*, log ε = 3·7 at 2200 A.). This difference can only mean that allylic bromide absorption has been replaced by alkyl bromide absorption, *i.e.*, hydrogen bromide addition may have occurred at the nearer, but not at the further, double bond in (I; X = Br). In accordance with the orientation of peroxide-catalysed hydrogen bromide addition to allyl bromide (Kharasch and Mayo, *J. Amer. Chem. Soc.*, 1933, **55**, 2468), the resulting product will be the same as that obtainable from (II; X = Br), *viz.*, **4 : 6-*dibromohex*-1-*ene***.

1 : 6-*Dibromohex*-2 : 4-*diene* (IV; X = Y = Br).—The residue left after isolating the diallyl monobromide from preparation (*c*) gave on further fractionation : (3) a monobromide-dibromide mixture, b. p. 49—87°/12 mm. (8 g.); (4) an isomeric dibromide mixture, b. p. 40—60°/0·03 mm. (14 g.); (5) 1 : 6-dibromohex-2 : 4-diene, b. p. 60—65°/0·03 mm., m. p. 86° from light petroleum (b. p. 40—60°) (Found : C, 30·1; H, 3·4. Calc. for $C_6H_8Br_2$: C, 30·0; H, 3·3%). This dibromide exhibited typical conjugated-diene light absorption in the ultra-violet region ($\lambda_{max.}$ 2550 A., ε = 20,000); the infra-red spectrum showed no absorption at 915 and 990 cm.$^{-1}$, but very strong absorption at 965 cm.$^{-1}$. A better synthesis is : diallyl monobromide (2 g.), *N*-bromosuccinimide (2·1 g.), carbon tetrachloride (12 ml.), and benzoyl peroxide (0·01 g.) are refluxed for 6 hours; removal of volatile material under reduced pressure leaves a residue (1·6 g.) which solidifies on cooling and then has m. p. 86° (after crystallisation from light petroleum) (Found : C, 30·4; H, 3·6%).

Hexa*-1 : 5-*diene*-3-*carboxylic Acid (I; X = CO_2H).—Diallyl monobromide (10 g.) in dry ether (60 ml.) was added during 2·5 hours to a well-stirred mixture of magnesium turnings (5 g.) and ether (30 ml.). Reaction proceeded readily after initiation with a crystal of iodine. The solution of the Grignard derivative so obtained was poured quickly on powdered, solid carbon dioxide. After hydrolysis with ice and hydrochloric acid and isolation in the usual way through its sodium salt, ***hexa*-1 : 5-*diene*-3-*carboxylic acid*** was obtained (3·5 g.), b. p. 101—102°/12 mm. (Found : C, 66·9; H, 8·1%; equiv., 126·5. $C_7H_{10}O_2$ requires C, 66·7; H, 7·9%; equiv., 126). Its infra-red spectrum exhibits strong absorption at 915 and 990 cm.$^{-1}$, but no absorption at 965 cm.$^{-1}$ (contrast the parent bromide, p. 939). ***p*-Bromophenacyl *hexa*-1 : 5-*diene*-3-*carboxylate*** had m. p. 32—33° after crystallisation from aqueous ethanol (Found : C, 55·7; H, 4·9; Br, 24·6. $C_{15}H_{15}O_3Br$ requires C, 55·8; H, 4·7; Br, 24·8%).

* We are indebted to these authors for an advance copy of their publication.

1-*Ethoxyhexa*-2 : 4-*diene* (IV; X = H, Y = OEt).—Diallyl monobromide (15 g.), sodium ethoxide (48 g.), and ethanol (240 ml.) were refluxed together for 3 hours. Most of the alcohol was then distilled off, water (450 ml.) added, and the mixture extracted with ether. The product isolated from the ethereal extract was 1-*ethoxy*-2 : 4-*diene* (43%), b. p. 48—49°/9 mm., n_D^{20} 1·4615 (Found : C, 75·9; H, 11·2. $C_8H_{14}O$ requires C, 76·1; H, 11·2%). The ultra-violet spectrum is characterised by : $\lambda_{max.}$ 2250 A., ε = 25,000 (in ethanol). The infra-red spectrum shows strong absorption at 965 cm.$^{-1}$, but no absorption at 915 and 990 cm.$^{-1}$. When the alcoholysis of the bromide was carried out under rather milder conditions (refluxing for 2 hours and addition of water without distilling off the alcohol), an incompletely conjugated ether was obtained, having b. p. 48—52°/15 mm., n_D^{20} 1·4572 (Found : C, 76·0; H, 11·2%).

Degradation of 1-*Ethoxyhexa*-2 : 4-*diene*.—The fully conjugated ether (5 g.) in ethanol (100 ml.) containing Adams's catalyst (0·5 g.) was shaken with hydrogen at 30 lb. per sq. inch. ; *ca.* 2·3 l. of gas were absorbed in a few minutes, and no further absorption occurred during 4 hours. Isolation of the product in the usual way gave ethyl *n*-hexyl ether (4 g.), b. p. 143—145°/761 mm., n_D^{20} 1·4016 (Found : C, 73·4; H, 13·9. Calc. for $C_8H_{18}O$: C, 73·8; H, 13·9%). An authentic sample of ethyl *n*-hexyl ether had n_D^{20} 1·4017.

The hydrogenated ether (3 ml.) was refluxed with hydriodic acid (57%; 20 ml.) for 3 hours. After dilution of the cooled mixture with water, the product was recovered by ether-extraction and identified as *n*-hexyl iodide, b. p. 178°/753 mm. (2·1 g.), by conversion into *n*-hexyl*iso*thiuronium picrate, m. p. alone or mixed with an authentic specimen 156° (from ethanol) (Found : C, 40·2; H, 5·2; S, 8·0. Calc. for $C_{13}H_{18}O_7N_6S$: C, 40·2; H, 4·9; S, 8·2%).

THE BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
TEWIN ROAD, WELWYN GARDEN CITY, HERTS.

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190. *The Reaction of Oct-1-ene with N-Bromosuccinimide.*

By L. BATEMAN and J. I. CUNNEEN.

The bromination of oct-1-ene with *N*-bromosuccinimide yields a monobromide mixture analogous to that given by hexa-1 : 5-diene (preceding paper) : 1-bromo-oct-2-ene and 3-bromo-oct-1-ene are the major and minor constituents, respectively. The relative proportions of these isomers agree closely with the equilibrium mixtures formed (at 100°) by certain homologous bromides (Young, Richards, and Azorlosa, *J. Amer. Chem. Soc.*, 1939, **61**, 3070).

Different proportions of the corresponding methyloctenes are formed (*a*) by treating the bromide with methylmagnesium iodide, and (*b*) by treating the derived Grignard derivative with methyl iodide. The product from the latter reaction is structurally similar to the octene dimer produced in a Grignard coupling reaction ; the significance of this finding is discussed.

The known ready interconversion of allylic bromides under the conditions of Ziegler bromination necessarily implies the isolation of an equilibrium mixture of the isomeric bromides. Any interpretation of the mechanism of the reaction based on the composition of the product is therefore valueless. However, this limitation is not generally appreciated, and hence the principles governing the composition of reaction products in allylic systems are reviewed.

IN the preceding paper, it was shown that the monobromination product obtained from hexa-1 : 5-diene (diallyl) by *N*-bromosuccinimide consisted of 1-bromohexa-2 : 5-diene containing *ca.* 10% of the isomeric 3-bromohexa-1 : 5-diene. Predominant substitution of the bromine atom at a terminal carbon atom and displacement of the relevant double bond were established unequivocally by infra-red spectrographic measurements, and by diagnostically significant substitution of the bromine by ethoxyl ions and identification of the resulting ether. However, the presence in diallyl of the second CH_2:CH group which remains unaffected in the monobrominated product renders the demonstration of the double-bond displacement by infra-red spectral variations far less striking, and analysis of the isomeric bromide mixture far less straightforward, than would be the case with a singly unsaturated Δ^1-olefin. A parallel investigation of the bromination of oct-1-ene is therefore reported here.

For reasons not understood (preceding paper), oct-1-ene reacts far more readily with *N*-bromosuccinimide than does diallyl, and in boiling carbon tetrachloride containing a little benzoyl peroxide reaction is complete within 15 minutes. Analytically pure octene monobromide * boils over a range of about 8° and exhibits infra-red absorption which affords detailed information about its composition. In contrast to the parent hydrocarbon (I; X = H), strong absorption occurs at 965 cm.$^{-1}$, while absorption at 924 and 990 cm.$^{-1}$ is much weaker. The 965 cm.$^{-1}$

(I.) CH_2:$[CH_2]_4$·CHX·CH:CH_2 $\qquad$ CH_2:$[CH_2]_4$·CH:CH·CH_2X (II.)

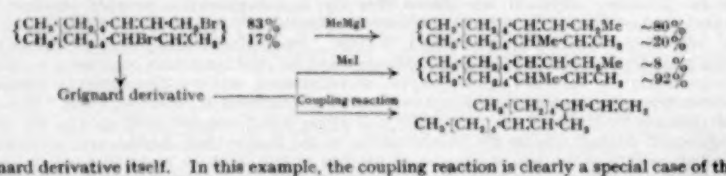
band specifies the presence of CHR:CHR′; the later bands denote a reduction in the concentration of CH_2:CHR groups. Quantitative comparison of the molecular extinction coefficient

* Throughout this paper "octene monobromide" designates the isolated *substitution* product irrespective of its isomeric composition.

at 924 cm.$^{-1}$ of a typical reaction product of the boiling range given above with that found for the parent hydrocarbon showed the sample to consist of a mixture of *cis*- and *trans*-1-bromo-oct-2-ene (II; X = Br) and of 3-bromo-oct-1-ene (I; X = Br), containing 17 ± 3% of the latter. The proportions of the 1-bromo-Δ^2- and the 3-bromo-Δ^1-isomer in this mixture agree exactly (within experimental error) with the measured compositions of the homologous butenyl, pentenyl, and hexenyl bromides equilibrated at 100° (Young, Richards, and Azorlosa, *J. Amer. Chem. Soc.*, 1939, **61**, 3070) in which the 3-bromo-Δ^1-isomers are present to the extent of 14·5, 19·9, and 14·2%, respectively. The boiling-point variation is obviously indicative of partial isomeric separation on distillation; as with diallyl (preceding paper), differences in the infra-red spectra and refractive indices of small head and tail fractions demonstrated the accumulation of the 3-bromo- and 1-bromo-isomers in the lower- and higher-boiling material, respectively.

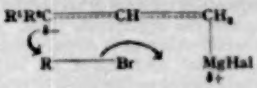
Carboxylation of the Grignard derivative of the octene bromide mixture yields homogeneous *oct-1-ene-3-carboxylic acid* (I; X = CO_2H) (p-*bromophenacyl* ester, m. p. 47—47·5°) which displays no infra-red absorption at 965 cm.$^{-1}$, but absorbs at 915 and 990 cm.$^{-1}$ with an intensity practically identical with that observed with oct-1-ene. This conversion of a bromide existing mainly in the primary allylic form (II) into an acid having entirely the secondary allylic structure (I) parallels exactly the behaviour of butenyl (Lane, Roberts, and Young, *J. Amer. Chem. Soc.*, 1944, **66**, 543) and geranyl (Barnard and Bateman, *J.*, 1950, 932) halides.

Reaction of the heterogeneous bromide with methylmagnesium iodide yielded a nonene mixture of (I; X = CH_3) and (II; X = CH_3) in proportion similar to those of the bromides. This finding is somewhat at variance with the product composition reported for the reaction between ethylallyl bromide (of unknown isomeric composition) and ethylmagnesium bromide (Prévost, *Compt. rend.*, 1928, **187**, 946; Prévost and Daujat, *Bull. Soc. chim.*, 1930, **47**, 588). Apart from any difference characteristic of the individual systems, the analytical procedure adopted by these authors (separate isolation and identification by oxidative degradation of the pure isomers) would appear to be quantitatively uncertain—a criticism which receives support from a similar discrepancy between the proportion of isomers produced in the Grignard coupling reaction of ethylallylmagnesium bromide as thus determined (Prévost and Richard, *Bull. Soc. chim.*, 1931, **49**, 1368) and the corresponding proportion obtained from crotylmagnesium bromide as carefully analysed by Young, Roberts, and Wax (*J. Amer. Chem. Soc.*, 1945, **67**, 841). In contrast, reaction of the Grignard derivative of the bromide with methyl iodide yielded a nonene mixture of quite different isomeric composition, the proportion of (II; X = Me) now being very small (*ca.* 8%). A similar result is derived from the structure of the hydrocarbon dimer isolated from the Grignard derivative, which proved to be essentially the unsymmetrical 6-vinyltetradec-8-ene. The reaction scheme summarises the results, which have a significant bearing on the mechanism of the coupling reaction and consequently on the nature of the



Grignard derivative itself. In this example, the coupling reaction is clearly a special case of the decomposition of the Grignard compound by an alkyl halide, and illustrates the tendency of allylmagnesium halides to behave as if the MgHal unit were attached to the secondary (or tertiary) allylic, rather than to the primary allylic, carbon atom (Roberts and Young, *J. Amer. Chem. Soc.*, 1948, **1472**, **68**; cf. *J.*, 1950, 932). This characteristic, which is not shared by the parent allylic halides (as the reaction now reported with methylmagnesium iodide demonstrates) could be taken as evidence that the MgHal group is actually attached to the secondary (or tertiary) carbon atom. However, Young and Roberts (*loc. cit.*) have carefully considered, and rejected, this deduction, and their arguments, although similarly inconclusive, appear very convincing. Accordingly, we interpret the mechanism of those reactions leading specifically to rearranged derivatives in terms of the intense polarity of the C–Mg bond. This polarity creates centres of high nucleophilic potential at both primary and secondary (or tertiary) carbon atoms, but since incipient ionisation of the MgHal group will be favoured by distribution of the unlike charges, reactivity at the latter position will be enhanced. Also, in reactions with alkyl halides or carbonyl compounds, the electrophilic power of the semi-cationic MgHal unit

will powerfully assist the necessary polarisation of these reagents in a process sterically conducive to the mutual development of the complementary electronic displacements :



Factors enhancing the importance of alternative decompositions, and thus leading to greater complexity of reaction products in certain substituted allylic systems, are discussed elsewhere (*J.*, 1950, 932).

Correlation between Reaction Mechanisms and the Composition of Products in Allylic Systems.—The contribution of the data recorded in this and the preceding paper to the understanding of the mechanism of Ziegler bromination and related reactions merits consideration, particularly as Dewar (" The Electronic Theory of Organic Chemistry," Oxford, 1949, p. 273) has recently presented a misleading argument that confirmatory evidence for a free-radical reaction mechanism would be obtained if 1-bromo-Δ^2-compounds were found to be the major products in the systems now considered.* We agree that certain features of the reaction as now conducted, *viz.*, marked catalysis by benzoyl peroxide and by ultra-violet light, afford almost compelling evidence for this type of mechanism, and the chain reaction first suggested by Bloomfield (*J.*, 1944, 114) is highly plausible. Quite definitely, however, our identification of the monobromides isolated from diallyl (preceding paper) and oct-1-ene as equilibrium mixtures of the allylic isomerides offers no critical information about the course of the primary substitution process. As emphasised in a discussion of anionotropy and related reactions (Catchpole, Hughes, and Ingold, *J.*, 1948, 8; de la Mare, Hughes, and Ingold, *ibid.*, p. 17), reaction products from interconvertible isomeric systems have significance in a mechanistic sense only when they are representative of *kinetic* as distinct from *thermodynamic* control, *i.e.*, the products formed in the reaction concerned are stable towards isomerisation under the conditions of reaction and subsequent isolation. Dewar dismisses the possibility of interconversion of the bromides resulting from Ziegler bromination in the sentence " Since the reaction is carried out in a non-polar solvent, the product cannot be formed by anionotropic rearrangement. . . . ." If " anionotropic rearrangement " here denotes a process in which free bromide and carbonium ions participate, this statement is literally true, but it is quite unrelated to the facts concerning the ease of isomerisation of allylic bromides (Young *et al.*, *loc. cit.*) and accordingly is irrelevant. The isomeric mobility of the liquid bromides is such that to obtain the pure isomers separately very careful and efficient fractionation at temperatures below *ca.* 20° is required. Reversion of the pure compounds to mixtures occurs readily on warming, and contaminants such as hydrogen bromide or peroxides—both of which are present in the reactions now considered—are powerful catalysts which facilitate this change even at room temperature (Kharasch, Margolis, and Mayo, *J. Org. Chem.*, 1936, **1**, 393; Young *et al.*, *loc. cit.*; unpublished observations by Mr. D. B. England working in Professor Ingold's laboratory). The remoteness of kinetic control over the products isolated from the *N*-bromosuccinimide reactions also becomes obvious by reference to other systems involving bromine addition to allylic systems, *viz.*, the combination of butadiene with bromine (Farmer, Lawrence, and Thorpe, *J.*, 1928, 729) and hydrogen bromide (Kharasch *et al.*, *loc. cit.*). In these cases, the futility of attempting to ascertain the initial proportions of **1 : 2**- and **1 : 4**-addition from experiments performed in boiling carbon tetrachloride would be universally recognised.

This aspect apart, the isolation of two isomeric diallyl or octene bromides in proportions approximating to their thermodynamic equilibrium proportions indicates that primary reaction products are not being considered. Thanks largely to work by Hughes and Ingold and by Young and their collaborators, some important principles correlating the composition of the products with reaction mechanism in allylic systems have recently become apparent. If we ignore certain special exceptions and modifications,† these, briefly, require : (i) that replacement

* Even more recently, Sutton and Datta (*J.*, 1949, 939) have attempted to draw mechanistic conclusions from the composition of the bromine-containing products of unknown heterogeneity derived from oleic, linoleic, and linolenic esters.

† *N.B.* (*a*) The possible accompaniment of an S_N2' with an S_N2 mechanism (cf. Barnard and Bateman, *J.*, 1950, 926). This is, however, difficult to realise deliberately, and circumstances conducive to its occurrence are well appreciated (Catchpole, Hughes, and Ingold, *loc. cit.*).

(*b*) Since there will be no sharp division between the conditions designated (i) and (ii), examples where " kinetically " free entities are unable to assume completely their equilibrium configurations are conceivable (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979). This phenomenon is mani-

of an allylic substituent in a reaction where the allylic residue (ion or radical) is without free existence leads to an isomerically homogeneous product; and (ii) that in a similar replacement where the allylic residue has free existence a mixture of isomerides results such that the proportion of the less stable isomer much exceeds the equilibrium value. As the theoretical basis of this behaviour and a wide survey of its ramifications have already been presented (Catchpole, Hughes, and Ingold *loc. cit.*; de la Mare, Hughes, and Ingold, *loc. cit.*), it remains here only to cite certain examples pertinent to the investigations described in this and the preceding papers.

Product compositions governed by conditions (i) are clearly discernible in the interactions of allylmagnesium halides with carbonyl compounds (see, *e.g.*, *J.*, **1950**, 932), where secondary (or tertiary) allylic derivatives are obtained irrespective of whether the Grignard complex is prepared from either form of pure halides or from mixtures (Young and Roberts, *J. Amer. Chem. Soc.*, **1945**, **67**, 148). As Young and Roberts argue, the definite structural course of these reactions implies a specific bimolecular transition state. A similar factor undoubtedly operates in the reactions between diallyl or allylbenzene and maleic anhydride or azodicarboxylic ester, where the isolated 1 : 1 adducts consist solely of hexa-1 : 4-diene or propenylbenzene (cinnamyl) derivatives (Alder, Pascher, and Schmitz, *Ber.*, **1943**, **76**, 27). Since the free-radical reaction mechanism postulated by Alder *et al.* cannot be seriously maintained on the evidence presented,* it is probably true, as the composition of the product indicates, that the reaction proceeds through an olefin–addendum complex, probably of the type envisaged for Diels–Alder reactions (see Koch, *J.*, **1948**, 1111).

The alternative method of reaction (ii) was considered by Hughes, Ingold, and their co-workers (*loc. cit.*) for examples involving ionic allylic intermediates. Allylic free radicals should necessarily exhibit the same general behaviour, for this merely reflects commonly accepted concepts concerning mesomeric entities. Few comparative data exist, but the following are illustrative. (*a*) In methylallyl halides, the equilibrium proportion of the minor constituent, the 1-methylallyl isomer, is about 10—15% between 0° and 100° However, in reactions of the mesomeric methylallyl cation with nucleophilic addenda, combination occurs to the extent of 55% at the primary, and 45% at the secondary, allylic carbon atom:

$$\left\{\begin{matrix}\text{CHMe:CH·CH}_2\text{·Hal} & (\sim 85\text{—}90\%) \\ \text{Hal·CHMe:CH:CH}_2 & (\sim 10\text{—}15\%)\end{matrix}\right\} \longrightarrow \text{Me·}\overset{\bullet}{\text{C}}\text{H:CH:CH}_2 \xrightarrow{\text{X}} \left\{\begin{matrix}\text{CHMe:CH·CH}_2\text{X} & (\sim 55\%) \\ \text{X·CHMe·CH:CH}_2 & (\sim 45\%)\end{matrix}\right\}$$

(equilibrium mixture) (non-equilibrium mixture)

(*b*) Autoxidation of ethyl linoleate (Bolland, *Proc. Roy. Soc.*, **1946**, *A*, **186**, 218) is a chain reaction in which the free radical formed by loss of a hydrogen atom from the CH_2 group of the 1 : 4-diene unit adds one molecule of oxygen, and the resulting peroxide radical then reacts with the parent ester to produce a hydroperoxide and also the original substituted pentadienyl radical. Bolland and Koch (*J.*, **1945**, 445; cf. Lindberg, Chipault, and Hendrickson, *J. Amer. Oil Chemists' Soc.*, **1949**, **26**, 109) have determined the extent to which oxygen adds centrally or terminally to the pentadienyl radical by estimating spectrographically the proportion of conjugated diene in the hydroperoxide formed; approximately 70% † of the oxidised molecules possess the rearranged structure:

$$\text{CH}_3\text{·[CH}_2\text{]}_4\text{·CH:CH·CH}_2\text{·CH:CH·[CH}_2\text{]}_7\text{·CO}_2\text{Et} \longrightarrow$$

$$\text{R·}\overset{\bullet}{\text{C}}\text{H·CH:CH·CH:CH·CH·R}' \longrightarrow \left\{\begin{matrix}\text{R·CH(O}_2\text{H)·CH:CH·CH:CH·R}' \\ \text{R·CH:CH·}\overset{+}{\text{C}}\text{H·CH(O}_2\text{H)·R}'\end{matrix}\right\} \sim 70\%$$

$$\text{R·CH:CH·}\overset{+}{\text{C}}\text{H(O}_2\text{H)·CH:CH·R}' \quad \sim 30\%$$

The small preponderance of free-radical activity at the terminal carbon atoms thus demonstrated is to be contrasted, in the same way as in (*a*), with the fact that thermal- or alkali-induced isomerisation of *equivalently substituted* 1 : 4- to 1 : 3-diene molecules proceeds nearly to completion.

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fested in the partial retention of activity by the products of S_N1 reactions of certain optically active halides (Bateman *et al.*, *loc. cit.*); in radical chain reactions it will clearly tend to intrude if environmental factors render the life of a radical abnormally short.

* A free radical reaction, catalysed by benzoyl peroxide occurs between natural rubber and maleinimides at a much lower temperature than the olefin–maleic anhydride reactions now referred to (Delalande, *Proc. International Congress of Pure and Applied Chem.*, London, 1947, in the press).

† In their publication, Bolland and Koch gave this figure as 70—85% owing to uncertainty as to the characteristic extinction coefficient of the pure conjugated diene. More recent data (Bergström and Holman, *Nature*, **1948**, **161**, 55) have largely resolved the uncertainty. We are indebted to Dr. Koch for informing us of the figure quoted.

Although data sufficiently accurate for significant comparison cannot be quoted, similar rearrangement occurs in reactions involving simple allylic radicals: a physical implication of the comparably high resonance energies of the two types of radical (allyl, 19 kcals./g.-mol.; pentadienyl, 30 kcals./g.-mol., Bolland and Ott, *Trans. Inst. Rubber Ind.*, 1945, **21**, 133) is that the similarity should be roughly quantitative, and the behaviour of allylic cations described under (*a*) affords convincing, if indirect, corroboration. Therefore, if bromination of Δ^1-olefins with *N*-bromosuccinimide proceeds by a radical chain mechanism we should expect a mixture of the 1-bromo-Δ^2- and 3-bromo-Δ^1-compounds to be formed in which the proportion of the latter is substantial, *i.e.*, probably *ca.* 40%, and certainly far more than the proportion present in the equilibrium mixture. Clearly then, the isolation of isomeric bromides from the diallyl and oct-1-ene reactions in relative amounts numerically the same as their equilibrium proportions, far from offering confirmatory evidence, is not directly related to such a mechanism.

Experimental.

Purchased oct-1-ene of American origin was found to contain <1% of non-terminal unsaturation. Fractionation through a Fenske-type column yielded a substantial fore-fraction, b. p. 120·1°/745 mm., free from this impurity.

Reaction of Oct-1-ene with N-Bromosuccinimide.—Oct-1-ene (112 g., 1 g.-mol.), *N*-bromosuccinimide (preceding paper) (63 g., 0·35 g.-mol.), carbon tetrachloride (200 ml.), and benzoyl peroxide (0·2 g.) were refluxed for 20 minutes, during which the imide reacted completely. When the product was worked up as usual, a liquid (63 g.) was obtained which on fractionation gave the following mixtures of 1-bromo-oct-2-ene (II; X = Br) and 3-bromo-oct-1-ene (I; X = Br): (1) 15·3 g., b. p. 71—73°/10 mm., n_D^{25} 1·4462 (Found: C, 50·3; H, 7·9; Br, 42·1. $C_8H_{15}Br$ requires C, 50·3; H, 7·9; Br, 41·9%); (2) 24·8 g., b. p. 73—79°/10 mm., n_D^{25} 1·4766 (Found: C, 50·1; H, 7·9; Br, 42·2%).

Infra-red Spectrographic Examination of Octene Monobromide.—Fractions (1) and (2) exhibited strong absorption at 965 cm.$^{-1}$ (in contrast to the parent olefin which is non-absorbing at this frequency) and weaker absorption at 924 cm.$^{-1}$ and 990 cm.$^{-1}$.

Quantitative estimation of the isomeric composition of the bulked product was carried out as described for diallyl monobromide (preceding paper). The presence of *cis*- and *trans*-1-bromo-Δ^2-isomer was again evident, but in the present example the fact that the compounds possess only one olefinic centre renders measurement of the concentration of the component $CH_2{:}CHR$ groups, *i.e.*, of 3-bromo-oct-1-ene, much more sensitive than with the mixture of substituted hexa-1 : 4- and hexa-1 : 5-dienes. The relevant data are:

Frequency, cm.$^{-1}$.	Molecular extinction coefficient: observed.	standard.	3-Bromo-oct-1-ene, %.	*trans*-1-Bromo-oct-2-ene, %.
924 *	20	117	17±3	—
965	66	150	—	44

* The strong absorption occurring maximally at 965 cm.$^{-1}$ partly overlaps the 990 cm.$^{-1}$ absorption band, and thus prevents an equivalent estimate of the $CH_2{:}CHR$ group concentration being derived.

The presence of *cis*-1-bromo-oct-2-ene (the above analysis indicates about 40%) was confirmed qualitatively by the existence of a broad absorption band at 680 cm.$^{-1}$.

Oct-1-ene-3-carboxylic Acid (I; X = CO_2H).—Octene bromide (20 g.) in dry ether (100 ml.) was added very slowly (during 2·5 hours) to magnesium turnings (8·5 g.) and ether (45 ml.). On completion of reaction (which proceeded steadily after initiation with a crystal of iodine) the solution was poured rapidly on a well-stirred excess of powdered carbon dioxide. The acidic product isolated by the usual procedure through its sodium salt proved to be the pure *oct-1-ene-3-carboxylic acid* (8 g.), b. p. 128°/11 mm. (Found: C, 69·0; H, 10·2%; equiv., 154. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%; equiv., 156). Its infra-red spectrum displayed no absorption at 965 cm.$^{-1}$ (indicating the complete absence of CH:CH groups), but strong absorption at 915 and 990 cm.$^{-1}$. *p-Bromophenacyl oct-1-ene-3-carboxylate* had m. p. 47—47·5° after crystallisation from aqueous ethanol (Found: C, 57·9; H, 6·1; Br, 22·8. $C_{17}H_{21}O_3Br$ requires C, 57·8; H, 6·0; Br, 22·7%).

Methyloctenes.—(*a*) *From octene monobromide and methylmagnesium iodide.* Octene monobromide (10 g.) in dry ether (15 ml.) was added during 20 minutes to a slight excess of methylmagnesium iodide in ether (30 ml.). A vigorous reaction occurred after each addition of the bromide solution. When addition was complete the reaction mixture was refluxed for 15 minutes, then cooled, and treated with aqueous ammonium chloride, and the product isolated in the usual way. The following mixtures of non-3-ene (II; X = Me) and 3-methyloct-1-ene(I; X = Me) resulted: (1) 2·2 g., b. p. 130—134°/754 mm., n_D^{15} 1·4210 (Found: C, 85·5; H, 14·3. Calc. for C_9H_{18}: C, 85·7; H, 14·3%), and (2) 2·9 g., b. p. 134—136°/754 mm., n_D^{15} 1·4216 (Found: C, 85·6; H, 14·3%). The isomeric composition of these fractions was found by infra-red spectroscopic examination to correspond closely to that of the original bromide: (1) contained 15—20%, and (2) 10—15%, of the Δ^1-isomer. Since the nonene isomerides are certainly not interconvertible under the reaction conditions, this finding provides sound evidence that methyl group substitution by this process occurs at the carbon atom bearing the displaced bromine atom.

(*b*) *From octenylmagnesium bromide and methyl iodide.* To an ethereal solution of octenylmagnesium bromide (prepared as described above from 7 g. of the halide) was added methyl iodide (6 g.) in ether (10 ml.) dropwise. Vigorous interaction occurred. When all the methyl iodide solution had been added, the mixture was refluxed for 10 minutes, and the product isolated in the usual way. A non-3-ene–3-methyloct-1-ene mixture different from that produced in (*a*) was obtained, *viz.*, 2 g., b. p. 118—120°/747 mm., n_D^{15} 1·4130 (Found: C, 85·6; H, 14·5. Calc. for C_9H_{18}: C, 85·7; H, 14·3%). From the

infra-red absorption intensities at 910 and 990 cm.$^{-1}$ (strong) and at 965 cm.$^{-1}$ (weak), the concentration of 3-methyloct-1-ene was estimated to be *ca.* 92%.

Dimerised Octene.—The Grignard derivative prepared from 6 g. of octene monobromide was refluxed in ether for 10 minutes, cooled, and decomposed with ice and dilute hydrochloric acid, and the product collected in the usual way and fractionated. After a fore-run of some octene, a fraction, b. p. 135—136°/13 mm., n_D^{20} 1·4503 (Found: C, 86·5; H, 13·7. $C_{16}H_{32}$ requires C, 86·4; H, 13·6%) (3 g.), was collected. The near constancy of the boiling point offers strong evidence of structural homogeneity, and, since the relative intensities of infra-red absorption at 965, 910, and 990 cm.$^{-1}$ indicate that CH_2:CHR and CHRCHR groups are present in similar concentration, this hydrocarbon is considered to be **9-*vinylistradec-6-ene***, possibly contaminated with a small amount of isomer.

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British Rubber Producers' Research Association,
48 Tewin Road, Welwyn Garden City, Herts.

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191. *The Uptake of Alkali Metals by Bacteria.*

By T. C. N. Carroll, C. J. Danby, A. A. Eddy, and Sir Cyril Hinshelwood.

By means of radio-active tracers the uptake of potassium, rubidium, and sodium ions by a strain of *Bact. lactis aerogenes* growing on a single synthetic medium has been investigated.

The heaviest growth is supported by potassium, but the cells can also take up rubidium and they can accumulate potassium and rubidium in the ratio 5:2 from a medium containing roughly equal concentrations of these two ions. They are, however, unable to take up detectable amounts of sodium from a mixture of sodium and rubidium. The accumulation of rubidium in the bacteria under the conditions of the test amounted to about 60% of the total present. Previous work has shown the corresponding figure for potassium to be 97%.

That the ion which actually finds its way into the cells is really rubidium was verified by measuring the radio-active decay constant of bacteria grown in presence of active rubidium and subsequently dried.

It has previously been shown (Danby, Eddy, and Hinshelwood, *Proc. Roy. Soc., B*, 1950, **136**, 544) that, as might be expected from much previous work on cells of different kinds, the presence of potassium is essential for the growth of *Bact. lactis aerogenes* in various synthetic media containing simple carbon and nitrogen sources. (References to the work of Conway and O'Malley, Leibowitz and Kupermintz, Pulver and Verzar, and others are given in the publication cited.) With the available chemical reagents an amount of potassium sufficient to support a small bacterial population (60 millions/ml.) was always present but further additions of potassium chloride increased this population linearly. Of the other alkali ions, rubidium alone seemed capable of filling the rôle of potassium in the cell, additions of rubidium chloride raising the population, though less effectively than did corresponding amounts of potassium chloride.

A detailed study of the relations between the bacterial population and the initial hydrion and potassium concentrations in glucose–ammonium sulphate media showed that hydrion antagonises the action of potassium. The facts were confirmed by measurements of the uptake by the cells of the radio-active isotope ^{42}K. In the range where the population was dependent on the potassium concentration the bacteria could take up 97% of the potassium available in the medium. This could be washed out of the cells by acid.

In the present work these observations have been confirmed and extended. In the first place, proof was desired that rubidium did in fact enter the cells and that the growth had not been due to impurities of potassium. ^{86}Rb was therefore added to the medium. From measurements of the activity of the final culture before and after centrifugation and from the activity of the separated bacteria, it was shown that radioactivity was present in the cells. The magnitude of the decay constant, moreover, confirmed that this was in fact due to rubidium. In the second place, comparisons were made of the uptake of the three ions sodium, potassium, and rubidium by use of the appropriate isotopes. The result showed that rubidium can be taken up in competition with potassium but less readily, while sodium is not taken up at all from a mixture of sodium and rubidium.

Methods.—The methods for the cultivation of the bacteria were those previously described (reference above), a standard strain of *Bact. lactis aerogenes* being maintained by serial subculture at 40·0° in a medium containing glucose, ammonium sulphate, magnesium sulphate, and an ammonium phosphate buffer. For the experiments to be described suitable additions of the appropriate alkali metals were made to the medium as required. The changes in cell population were determined by a turbidimetric technique calibrated with suspensions of known count.

The radio-active alkali metals were obtained by neutron irradiation of the carbonates at A.E.R.E., Harwell. The weighed samples of active materials were neutralised with the calculated quantity of acid and standard solutions made up. From activity measurements on these standards and the known half-lives of the radio-elements the relation between the observed rate of count of a sample at any time and the concentration of the corresponding alkali metal could be obtained.

The activity measurements were made with a liquid-type Geiger counter of about 10-ml. capacity. The electronic counting equipment followed conventional lines and was built in the laboratory. The recovery time of each Geiger tube was measured with a calibrated oscilloscope and a paralysis–time circuit in the amplifier set to a value some 10% greater, the appropriate corrections being applied to the observed rates of count.

The problem arose of determining the activity of a bacterial suspension which had been separated from an active supernatant liquid. Since it is impossible to remove all adhering fluid by centrifugation, and washing of the cells is not permissible, a method similar to the method of residues in phase-rule studies was adopted. For example, 10 ml. of a suspension were centrifuged and 9 ml. of the cell-free supernatant liquid taken for test. The remaining 1 ml. was left with the cells. From a knowledge of the activity of this concentrated suspension and of the supernatant liquid itself the activity of the cells themselves is calculable.

The similarity between the half-lives of ^{24}Na (14·8 hours) and ^{42}K (12·4 hours), and the fact that they are both γ-emitters, makes it difficult to analyse a mixture of the two either by measurement of the decay curves or by absorption measurements. But each component in a mixture of ^{86}Rb and ^{24}Na, or of ^{24}Rb and ^{42}K, can be readily estimated, since ^{86}Rb is a simple β-emitter and has a half-life of 19·5 days. Accordingly, the form of the composite decay curves was used to determine the amounts of the individual ions taken up by cells grown on the one hand in mixtures of rubidium and sodium and on the other in mixtures of rubidium and potassium.

There is, in such experiments, the possibility that one of the various alkali ions, once they reach low concentrations in the medium, might be selectively taken up by the cells. It is even more likely that one or the other might suffer displacement by hydrion if the medium were allowed to become acid. To ensure that neither of these factors came into play conditions were so chosen that the maximum bacterial population which the medium could support was limited by the glucose concentration. At the value chosen there were always appreciable amounts of alkali ion remaining outside the cells, and the pH changed little from its initial value of 7·10.

Experimental.

(1) *Growth with Rubidium only.*—Tubes containing medium with the appropriate amounts of added active rubidium were inoculated and at the suitable stage of growth the contents were centrifuged, samples of 10 ml. being used. 9 Ml. of the supernatant liquid were drawn off, the remaining 1 ml. being left with the total amount of cell material. The samples were tested in a liquid counter, the original culture and the separated cells after dilution in a known ratio so as to obtain a convenient counting rate (4000—10,000 counts/minute), and the supernatant liquid after being made up to a standard volume with water. From the various counts and dilution factors the activity in cells and (supernatant liquid was calculated. Two independent values for the activity of the cells are obtainable, one from (separated cells with 1 ml. of liquid) and (supernatant liquid), the other from (total culture) and (supernatant liquid). The results are given in Table I (see next section).

The bacteria from one of the samples were washed and dried in a small aluminium dish, and the rate of count was determined at intervals over a period long enough to give the decay constant. The decay was compared with that of standard ^{86}Rb samples prepared from the stock solution directly.

(2) *Growth with Rubidium and Sodium.*—A culture medium was made up to contain approximately 10 g.-ions of active Rb and 5 g.-ions of active Na per l. The general procedure was then as described for the experiments with rubidium alone. The activities of total cultures, supernatant liquids, and separated cells were all measured (*a*) as soon as possible after growth and (*b*) after 5 days, by which time only the rubidium contributes appreciably to the total activity (^{24}Na and ^{42}K fall to about 10^{-4} of the initial activity in 6 days). By extrapolating back the readings from (*b*) one can obtain the activity due to Rb at the time of (*a*) and so the activity due to the ^{24}Na at that time. Both the activities are then extrapolated to that time at which the growth of the culture is deemed to have terminated. Factors for conversion of activity to concentration were obtained by measurements on the standard solutions and referred in each case to zero time. Results are given in Table II.

(3) *Growth with Rubidium and Potassium.*—Procedure was similar to that described under (2). The calculations are somewhat more elaborate since, in contrast with the previous case, the bacteria prove to contain both metals. The contribution from each to the activity of each kind of sample has to be worked out for various times. Extrapolation to zero time in the usual way is then possible. The results are given in Table III.

Results.

(1) *Rubidium.*—The measurements recorded in Table I are values corrected for the various dilution factors. The different horizontal lines refer to various cultures sampled when growth

had proceeded to a bacterial population which is expressed in the first column as a fraction of what the particular medium could have supported had time been allowed.

It is evident that the cells take up as much as 60% of the total rubidium supplied in the medium, but that after growth has ceased they give it up again. Previous experiments with potassium showed that the loss is due to the formation of acid in the medium by the continued fermentation of the glucose.

TABLE I.

Uptake of rubidium.

Medium contained : inactive potassium, 1·1 × 10^{-6} g.-ions/l. ; radio-active rubidium, 9·9 × 10^{-6} g.-ions/l. ; M/40-ammonium ion (buffer constituent).

Growth ceased at bacterial population of 240 millions/ml.

Bacterial population, % of max.	Activity of whole culture.	Activity of supernatant liquid.	Activity of cells + 1 ml. of liquid.	% of total Rb taken up by cells, direct.	by difference.
75	21·2	10·5	10·7	45·7	50·5
79	20·4	10·2	10·6	46·8	50·2
85	21·3	10·3	—	—	51·6
94	20·3	8·9	12·0	54·8	55·6
98	21·1	8·8	12·3	53·9	58·4
100	20·6	8·3	12·4	56·2	59·7
12 hrs. later	22·1	25·0	1·8	0	0
12 hrs. later	22·7	25·2	1·7	0	0

(All activities are given as counts/min. × 10^{-4}.)

TABLE (II).

Growth in presence of rubidium and sodium.

Medium also contained : inactive potassium, 1·1 × 10^{-6} g.-ions/ml. ; M/40-ammonium ion (buffer constituent).

Growth was restricted to about 100 millions/ml. by limitation of glucose, otherwise 200 millions/ml. would have been reached.

Alkali-metal concns., gm.-ions/l. × 10^6.				Alkali metal in cells (expressed as an equivalent concn. in the medium).			
Whole culture,		Supernatant liquid,		Direct measurement,		By difference,	
Rb.	Na.	Rb.	Na.	Rb.	Na.	Rb.	Na.
13·0	4·9	10·5	5·5	2·1	0	2·5	−0·6
12·6	6·3	10·4	6·3	—	—	2·2	0·0
11·9	6·5	10·0	7·9	1·7	0	1·9	(−1·4)

TABLE III.

Growth in presence of rubidium and potassium.

Medium also contained : inactive potassium, 1·1 × 10^{-6} g.-ions/l. ; M/40-ammonium ion (buffer constituent).

Growth was restricted to 200 millions/ml. by limitation of glucose, otherwise 400 millions/ml. would have been reached.

Alkali-metal concns. g.-ions/l. × 10^6.				Alkali metal in cells (expressed as equivalent concn. in medium).			
Whole culture,		Supernatant liquid,		Direct measurement,		By difference,	
Rb.	K.	Rb.	K.	K.	K.	Rb.	K.
9·9	10·9	6·1	2·9	2·7	5·6	3·8	8·0
8·9	13·8	5·1	2·9	—	—	3·8	10·9

The decay constant corresponding to a half-life of 19·9 days makes the identification of the alkali metal in the cells with rubidium quite certain.

(2) *Rubidium and Sodium.*—Here growth was limited by exhaustion of the glucose, the concentration of this being kept low to prevent fermentation at the end of growth. Consequently the total uptake of alkali is proportionately less than in (1). No sodium could be found in the cells in the direct test. The amount found by the difference method was either zero or, as a result of manipulative losses, negative (Table II).

(3) *Rubidium and Potassium.*—Here again growth was deliberately controlled by limitation of glucose supply so that rubidium and potassium should complete on approximately equal terms throughout. The total uptake is therefore far less than it could be. The amount of

rubidium consumed is approximately 40% of the potassium. The actual form of the radioactive-decay curves confirmed the presence of the two metals with their respective half-lives (Table III).

One of the authors (A. A. E.) is in receipt of a maintenance grant from the Institute of Brewing.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, December 22nd*, 1949.]

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192. *Germanium (Germanyl) Ferrocyanide.*

By M. PEISACH, W. PUGH, and F. SEBBA.

Ionised ferrocyanides react with acid solutions of germanium dioxide to form an insoluble white precipitate. The reaction can be used as a qualitative test for germanium and, under proper conditions, leads to a product of definite composition, namely *germanyl ferrocyanide*, $[Ge(OH)_2]_2Fe(CN)_6$ or $(GeO)_2Fe(CN)_6.2H_2O$.

INSOLUBLE ferrocyanides of quadrivalent titanium, zirconium, thorium, and tin are well known (Gmelin, "Handbuch der Anorganischen Chemie," 8th Edn., System No. 59, Part B, 1930, p. 604), but no corresponding compound of germanium has been described hitherto. Many years ago, one of us (F. S.) observed that a white precipitate appeared when an acid solution of germanium chloride was treated with potassium ferrocyanide. The nature of this precipitate and the conditions necessary for the preparation of *germanyl ferrocyanide* are now described.

The formation of a white precipitate, or even a colloidal opalescence, on treatment with ferrocyanide may well serve as a useful qualitative test for germanium. This element is usually associated in minerals with arsenic and is separated from other metals by distillation of the volatile chloride from hydrochloric acid solutions. However, even with the utmost precautions to keep arsenic in the quinquevalent state the distillate contains some arsenic which then inteferes with the simple test for germanium by precipitation as the white sulphide. Neither tervalent nor quinquevalent arsenic gives a precipitate with ferrocyanides (Gmelin, *op. cit.*, p. 607). Hence, if the distillate is treated with potassium ferrocyanide solution the appearance of a precipitate is evidence of the presence of germanium. One part of germanium in 10,000 parts of solution gives an opalescence; larger amounts give a white gelatinous precipitate.

The nature and appearance of this precipitate vary with the conditions. In slightly acid solution there may be a time lag of an hour or more before precipitation, but it is shortened by increasing the acidity of the solution and by raising the temperature; the optimum conditions appear to be an acidity at least equivalent to 4N-hydrochloric acid and a temperature of 50—60°. The appearance of opalescence or a precipitate, depending on the concentration of germanium, is then a matter of seconds. Sulphuric, acetic, and chloroacetic acid are much less effective in coagulating the initial sol; and if the temperature exceeds 70° the inital white precipitate becomes blue rather quickly.

This colour change is undoubtedly due to the formation of Prussian-blue by decomposition of the excess of ferrocyanide in the strongly acid solution (Gmelin, *op. cit.*, p. 584). It takes place slowly in the cold, even in the dark and in the absence of air, but rapidly if a large excess of ferrocyanide is employed. Consequently, in the early part of the work it was impossible to get a product of uniform composition. Later, it was found that if the ratio of ferrocyanide to germanium does not exceed one g.-ion per g.-atom the precipitate darkens only slowly during several days. This is fortunate because the gelatinous precipitate cannot be filtered off and, as it is highly retentive of adsorbed electrolytes, its washing by decantation and centrifugation occupies several days. Under the most favourable conditions encountered the final product had acquired a pale mauve tinge. This product was found to contain two atomic proportions of germanium for each ferrocyanide radical and its analysis corresponds with the empirical formula $(GeO)_2Fe(CN)_6.2H_2O$ or $[Ge(OH)_2]_2Fe(CN)_6$. *X*-Ray structure analysis is the only means of establishing unequivocally which is the actual structure. No compound even approximating in composition to $GeFe(CN)_6$ has been detected in this work, and this is in accord with the general chemistry of germanium, for there is no recorded compound of this element in which the occurrence of a simple quadrivalent germanium ion has been estalished.

A similar zirconyl ferrocyanide, $(ZrO)_2Fe(CN)_6$, has been described by Weiball (*Lunds Univ. Arsskr.*, 1881—82, II, 18, No. 5, 40), though Venable and Moehlmann (*J. Amer. Chem. Soc.*, 1922, **44**, 1705) obtained products with ferrocyanide–zirconyl ratios as high as 3 : 4. Our

experience with the germanium ferrocyanide leads us to suspect, however, that the American authors' products were highly contaminated with Prussian-blue.

Experimental.

Germanyl Ferrocyanide.—Pure germanium dioxide (4 g.) was dissolved in hot 5N-sodium hydroxide (100 ml.). The solution was diluted to 400 ml., filtered from a trace of undissolved oxide, neutralised with hydrochloric acid, and treated with concentrated hydrochloric acid to bring the acidity to 5N. The temperature was adjusted to 60°. Precipitation was made with 0·2M-potassium ferrocyanide (200 ml.).

The only practical way of washing the pure, white, bulky, and gelatinous precipitate was by settling and decantation. Because each settling period was of the order of a day the whole process of washing was extremely tedious and led to continuous darkening of the product. After the fourth wash the precipitate was dried *in vacuo* for several days, becoming then more granular. Further washing with water was then possible in a much shorter time and without appreciable decomposition. Finally, the moist precipitate was centrifuged 10 times with small amounts of ether to ensure complete removal of adsorbed hydrochloric acid. Alcohol could not be used for this purpose, for it tended to peptise the material. The product was then dried *in vacuo*.

It was a pale mauve powder which was quite stable in air and showed no tendency to become blue after many weeks' exposure to the laboratory atmosphere. Some samples that had been less thoroughly washed did become blue on storage. A thin film of Prussian-blue could often be seen over the surface of the precipitate in the centrifuge tube.

Analysis.—Germanium was determined as Mg_2GeO_4 by a modification of Muller's method (*J. Amer. Chem. Soc.*, 1922, **44**, 2493). Modification was necessary because *germanyl ferrocyanide* is insoluble in water and in acids. It does however dissolve in caustic alkalis and in aqueous ammonia. An ammoniacal solution of the sample was therefore treated with ammonium sulphate–magnesium sulphate solution, the proportions of the reagents being carefully controlled in accordance with Muller's directions. The precipitate of magnesium ammonium germanate, after being washed, was ignited to Mg_2GeO_4. The ferrocyanide in the filtrate from the germanium determination was determined, after acidification with sulphuric acid, by titration with standard permanganate by the method of de Haen (*Annalen*, 1854, **90**, 160) or with standard ceric sulphate using ferroin as internal indicator (Vogel, "Quantitative Inorganic Analysis," Longmans, 1947, p. 383). In a few cases too, the total iron was determined volumetrically after decomposition of a fresh sample with concentrated sulphuric acid (Kjeldahl). Excellent agreement was obtained by all methods.

In all, over 30 analyses were made of samples of 4 different preparations (Found: Ge, 34·2; $Fe(CN)_6$, 49·6; Fe, 13·0. $[Ge(OH)_3]_2Fe(CN)_6$ requires Ge, 34·2; $Fe(CN)_6$, 49·84; Fe, 13·1%).

Confirmation that the compound contains either co-ordinated water or hydroxyl groups was obtained by pyrolysis. A weighed sample, mixed with copper oxide to decompose volatile cyanogen compounds, was heated in a combustion train in pure dry air and the water liberated was absorbed in "Anhydrone." The water absorbed amounted to 8·6% (Calc. for $2H_2O$, 8·5%).

Properties.—Pure germanyl ferrocyanide is a white solid which, like all other ferrocyanides, is slowly decomposed by strong acids with formation of Prussian-blue. It is insoluble in water and in moderately strong acids, but dissolves readily in alkalis, with decomposition, forming soluble germanates and alkali ferrocyanides. Heat decomposes it; at 130° it loses about one-third of its weight, and the vapours smell strongly of cyanogen compounds; at a red heat in air it loses half its weight and the vapours carry germanium as well, probably the result of reduction by carbon to the volatile germanous oxide. When desiccated *in vacuo* over sulphuric acid it becomes extremely hygroscopic; it will then absorb up to one-third of its own weight of water.

University of Cape Town. [*Received, January 9th*, 1950.]

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193. *The Intramolecular Nature of the Benzidine Rearrangement.*

By G. J. Bloink and K. H. Pausacker.

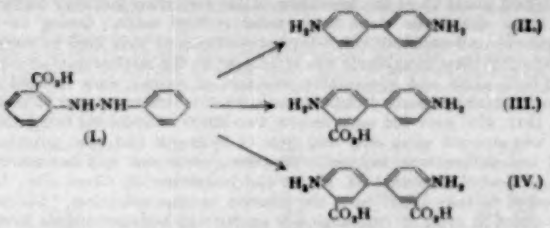
By a study of the rearrangement of unsymmetrical hydrazobenzenes, confirmation of the intramolecular nature of the benzidine rearrangement has been obtained.

Although there have been many formulations of the mechanism of the benzidine rearrangement (cf. Dewar, "Electronic Theory of Organic Reactions," Oxford, 1949, pp. 235 *et seq.*), there had hitherto only been one investigation (Ingold and Kidd, *J.*, 1933, 984) which determined whether the reaction was inter- or intra-molecular.

Ingold and Kidd rearranged a mixture of 2 : 2′-dimethoxy- and 2 : 2′-diethoxy-hydrazobenzene, and thermal analysis indicated that the only products were 3 : 3′-dimethoxy- and 3 : 3′-diethoxy-benzidine. Apparently no 3-methoxy-3′-ethoxybenzidine was formed in this mixed rearrangement and it was concluded that the reaction was intramolecular. As the above work depends for its conclusions on mixed melting points, it was decided to perform some experiments whereby a chemical separation of possible products could be attempted.

Accordingly, the various carboxy-substituted hydrazobenzenes were rearranged, and the

products examined. If one considers the rearrangement of 2-*carboxyhydrazobenzene* (I), the possible products are benzidine (II), 3-*carboxybenzidine* (III), and 3 : 3'-dicarboxybenzidine (IV).



If the reaction is intermolecular, the principal products should be (II) and (IV) as a large difference in reactivity would be expected between the two fragments formed by an N–N fission, whereas (III) only would be formed by an intramolecular reaction. Thus the presence of (II), provided that decarboxylation does not occur, should indicate an intermolecular reaction.

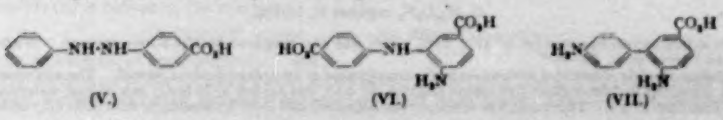
Now (II) can readily be chemically separated from (III) and (IV) owing to its non-solubility in sodium hydroxide, and thus its presence can be readily demonstrated. Furthermore, the alkali-soluble fraction will be either pure (III) or a mixture of (III) and (IV), and these two possibilities can be differentiated by both a nitrogen estimation and a determination of the acid equivalent.

The 2-, 3-, and 4-*carboxyhydrazobenzenes* were prepared by first condensing the appropriate primary amino-acid with nitrosobenzene to form the corresponding *carboxyazobenzene*. It may be noted that when either anthranilic acid or ethyl anthranilate was used, very poor yields of the azo-compound were obtained owing, apparently, to the sterically interfering *ortho*-group. These azo-compounds were then reduced to their hydrazo-analogues by means of zinc dust and sodium hydroxide, but the latter compounds were not isolated but were immediately rearranged by warming with added excess of dilute hydrochloric acid. After removal of any azo-compound by filtration, the reaction mixture was made alkaline and extracted with ether in order to isolate any benzidine formed. The alkaline solution was then weakly acidified and the amino-acids were precipitated by addition of glacial acetic acid.

It was found that a small yield of benzidine was obtained from the rearrangement of 2-carboxyhydrazobenzene (I), indicating the possibility of an intermolecular action. However, the amino-acid gave analyses (both for nitrogen and for acid equivalent) for the mono-acid (III) and not the di-acid (IV), indicating that the benzidine had been formed by a partial decarboxylation of (III) during the course of the reaction. As the results are not conclusive it was desirable to obtain further information from the behaviour of the other isomers.

When 3-carboxyhydrazobenzene was rearranged under the same conditions, no benzidine could be isolated from the reaction mixture and the amino-acid gave analyses corresponding to pure 2-*carboxybenzidine*. This clearly indicates that an intramolecular reaction is involved and the benzidine formed during the rearrangement of (I) has only resulted by decarboxylation occurring during the reaction.

It is also of interest that when 4-carboxy- and 4-carbethoxy-hydrazobenzene (as V) were rearranged, large yields of benzidine were obtained. If one assumes an intermolecular rearrangement, then by application of the rules enunciated by Dewar (*op. cit.*, p. 234), the main products should be benzidine (II) and 4' : 5-dicarboxysemidine (VI) along with some 5-carboxydiphenyline (VII). The amount of benzidine formed from the acid corresponded to a 74% yield if intermolecular reaction were assumed. However, the amino-acid fraction was found to be pure (VII) (nitrogen analysis and acid equivalent) and no indication of the presence of the dicarboxylic amino-acid (VI) was obtained. Thus the benzidine has once again merely resulted from a decarboxylation and not from an intermolecular reaction. This is substantiated by the fact that a gas was evolved during the rearrangement.



In order to obtain further evidence, it was intended to investigate compounds containing a hydroxyl group in place of the carboxyl group; so once again there would be an alkali-solubilising group present which would allow the separation of any benzidine that may be formed.

However, many difficulties were encountered in this work. Owing to their ease of preparation benzeneazo-β-naphthol and 4-hydroxyazobenzene were used as starting materials. When the reduction of these compounds was attempted by the method used above, fission of the $-N{=}N-$ bond took place and appreciable amounts of aniline were isolated in each case. Catalytic reduction in the presence of Adams's catalyst (cf. Strel'tsova and Zelinskii, *Bull. Acad. Sci. U.R.S.S.*, 1941, 401) gave the same results, two moles of hydrogen being absorbed; when the reduction was stopped when only one mole of hydrogen had been adsorbed, unchanged azo-compound and aniline were isolated. However, when zinc and ammonium chloride in benzene–aqueous alcohol were used (cf. Krolik and Lukaschevich, *Chem. Abs.*, 1949, **43**, 5774) reduction appeared to take place, since the solution became colourless. Dilute hydrochloric acid was then added in order to rearrange any substituted hydrazobenzene formed and, after evaporation of the benzene and alcohol, the reaction mixture was made alkaline and extracted with ether to remove any bases formed. Evaporation of this extract yielded an almost negligible amount of substance, in both cases, which did not give any tests for benzidine (insolubility of sulphate and immediate formation of dibenzylidene derivative in alcoholic solution) or aniline (diazotisation test). This result indicates that fission of the $-N{=}N-$ linkage had not occurred during this method of reduction, since aniline was not formed. In addition, the rearrangement had not produced benzidine, thus confirming the findings obtained with the carboxy-compounds. When the aqueous solution was made slightly acidic, and excess of sodium hydrogen carbonate added, the rearrangement product was precipitated. Owing to its rapid oxidation, it could not be obtained pure even though the whole reaction had been performed in an atmosphere of nitrogen.

In order to prevent oxidation of the rearrangement product (an amino-phenol) it was decided to use the benzhydryl ethers of benzeneazo-β-naphthol and 4-hydroxyazobenzene and to remove the protecting benzhydryl group by hydrogenolysis after rearrangement. The latter benzhydryl ether was readily obtained by treatment with diphenyldiazomethane in dry benzene, but the benzeneazo-β-naphthol was recovered unchanged when similarly treated. It was found that although the above ether was readily reduced, the solution rapidly darkened during rearrangement and, as the product appeared to resist hydrogenolysis, this method of approach was abandoned.

Our work thus confirms Ingold and Kidd's postulation that this reaction is intramolecular. Since this work was completed, Wheland and Schwartz (*J. Chem. Physics*, 1949, **17**, 425) have obtained confirmatory evidence by a study of the rearrangement of an unsymmetrical hydrazobenzene by using ^{14}C as a radioactive tracer.

Experimental.

(M. p.s are uncorrected. Analyses are by Messrs. N. Lottkowitz and N. Gamble.)

Carboxy-substituted Compounds.—Preparation of azo-compounds. Freshly prepared nitrosobenzene (Vogel, "A Text Book of Practical Organic Chemistry," Longmans, 1948, p. 603) was condensed with the appropriate amino-compound in ethyl alcohol and glacial acetic acid under the conditions described by Wieland (*Ber.*, 1915, **48**, 1098). The reaction mixture was concentrated to obtain an additional amount of azo-compound. With 2-carboxyazobenzene it was necessary to evaporate the reaction mixture to dryness and dissolve the residue in benzene. Unchanged anthranilic acid was removed by extraction with dilute hydrochloric acid, and crude 2-carboxyazobenzene with aqueous sodium hydrogen carbonate. The latter product was precipitated by acidification of the carbonate solution and, after being extracted with ether, was crystallised from light petroleum (b. p. 60—90°).

The following table summarises the pertinent data for these compounds:

Substituted azobenzene.	Yield, %.	M. p.	Crystal form.	Solvent.	N (found), %.
2-Carboxy-	11	91—92°	Yellow needles	Light petroleum (b. p. 60—90°)	12·3
3- ,, ...	21	169	Light orange prisms	Alcohol	12·7
4- ,, ...	56	247	Orange plates	Alcohol	12·2

$C_{13}H_{10}O_2N_2$ requires N, 12·4%.

4-Carbethoxyazobenzene (m. p. 87°; 27% yield) was also prepared by the above method. Wieland (*loc. cit.*) gives m. p. 86—87°.

Reduction of the substituted azobenzene and rearrangement of the hydrazobenzene formed. The azobenzene (5 g.), dissolved in 2·5N-sodium hydroxide solution (50 ml.), was heated (0·75 hour) in a boiling water-bath with zinc dust (7 g.). The colourless solution was decanted and 2·5N-hydrochloric acid (150 ml.) added,

whereupon a precipitate was obtained. Heating was continued (1 hour) and any solid present (identified as azo-compound formed by atmospheric oxidation) was filtered off. The solution was then basified and extracted with ether. The benzidine thus obtained was identified as its dibenzylidene derivative (m. p. and mixed m. p. 233°). The alkaline solution was acidified with acetic acid, the amino-acid fraction then being precipitated. It was purified by dissolution in hot dilute hydrochloric acid (charcoal) and precipitated as colourless micro-crystals by addition of excess of sodium acetate. If any zinc salts were present, they were removed by heating the solid with sodium hydrogen carbonate solution and the amino-acid was precipitated by addition of acetic acid. When 4-carbethoxyazobenzene was used, the reduction was carried out in alcoholic sodium hydroxide. Simultaneous hydrolysis took place, for the amino-acid obtained by rearrangement was identical with the product formed from 4-carboxyazobenzene.

The results obtained are summarised below :

Initial compound.	Azo-compound recovered, g.	Wt. of benzidine, g.	Wt. of amino-acid, g.	M. p. of amino-acid.	Acid equiv.	N (found), %.
2-Carboxy-	—	0·13	0·4	207—208° (d.)	232, 232	12·3
3-Carboxy- ...	—	—	2·5	269° (d.)	223, 226	12·7
4-Carboxy-	0·61	1·51	0·9	236—237° (d.)	224, 238	12·5
4-Carbethoxy-...	0·68	1·37	1·61	236—237° (d.)	224, 238	12·5

$C_{13}H_{13}O_2N_3$ requires N, 12·3%; equiv., 228. $C_{13}H_{12}O_4N_2$ requires N, 10·9%; equiv., 136.

Benzhydryl Ether of 4-Hydroxyazobenzene.—4-Hydroxyazobenzene (8·2 g.) was dissolved in dry benzene (160 ml.), and a solution of diphenyldiazomethane (9 g.) in benzene added. The solution was kept for 18 hours at 32° and then concentrated to 25 ml. The *ether* obtained (9·3 g.) crystallised from ethyl alcohol as yellow needles, m. p. 127° (Found : N, 8·0. $C_{25}H_{20}ON_2$ requires N, 7·7%).

UNIVERSITY OF MELBOURNE. [*Received, November 9th*, 1949.]

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194. *Optical Activity dependent on a Six-covalent Bivalent Osmium Complex.*

By F. H. BURSTALL, F. P. DWYER, and (MISS) E. C. GYARFAS.

The reaction between potassium osmichloride $K_2[OsCl_6]$ or ammonium osmibromide $(NH_4)_2[OsBr_6]$ and excess of 2 : 2′-dipyridyl at 260—280° yields the complexes [Os $Cl_2$2dipy]Cl,3H_2O and [Os 3dipy]Cl_2.6H_2O and the corresponding bromides after separation and crystallisation from water. The dark-green bivalent osmium complex is stable towards aqueous acids and alkalis and has been converted into the corresponding *iodide*, *perchlorate*, and *hydroxide*. By use of silver antimonyl tartrate optically active enantiomorphs of the *antimonyl tartrate* and the *iodide* have been obtained.

IT was shown some years ago by one of us (Burstall, *J.*, 1936, 173) that 2 : 2′-dipyridyl and ruthenium trichloride gave the well-defined stable salt [Ru 3dipy]Cl_2.6H_2O. The cation of this complex salt was sufficiently stable to be resolved into optically active forms by use of ammonium (+)- and (−)-tartrate. It has now been found that reaction of 2 : 2′-dipyridyl and potassium osmichloride and ammonium osmibromide at 260—280° results in reduction of the quadrivalent osmium salts to the tervalent and bivalent states with concurrent formation of the *chlorides* [OsCl_2 2dipy]Cl,3H_2O (I) and [Os 3dipy]Cl_2.6H_2O (II) or the corresponding *bromides*. The reactions of potassium osmichloride and ammonium osmibromide with 2 : 2′-dipyridyl are not, however, identical; the former gives a mixture of (I) and (II), except in presence of metallic osmium or other reducing agents which lead to (II) alone, whereas ammonium osmibromide gives almost entirely the bivalent osmium salt most conveniently isolated as the *iodide* [Os 3dipy]I_2.3H_2O (III).

The dark red tervalent chloride (I) has not been closely examined but it can be reduced to (II) by heating it with 2 : 2′-dipyridyl and osmium metal. The chloride (II) and other salts of the complex cation [Os 3dipy]$^{++}$ are very dark green, crystalline substances which give intensely coloured solutions, very dark green by reflected light and dark red by transmitted light, even at concentrations of 10^{-4}M. The complex ion is stable in strongly acid or alkaline solutions, but in nitric acid or concentrated sulphuric acid the colour changes to red, probably by oxidation, with formation of a tervalent osmium complex ion of the type [Os 3dipy]$^{+++}$. Oxidation is accomplished by reagents such as ceric sulphate. The complex ion acts as a reversible redox indicator, the reaction

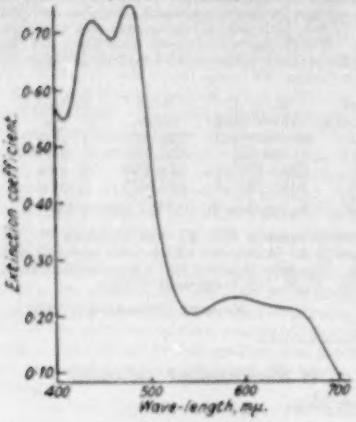
$$[\text{Os 3dipy}]^{++}\ (\text{green}) \longrightarrow [\text{Os 3dipy}]^{+++}\ (\text{red}) + e^-$$

having a potential of approximately 1 volt.

The separation of the optically active forms of the iodide [Os 3dipy]I_2.3H_2O was carried out through the corresponding *antimonyl tartrate* but could be achieved, although less effectively,

through the (+)-*tartrate* as with the analogous ruthenium derivative. The optically active antimonyl tartrates [Os 3dipy](SbOC$_4$H$_4$O$_5$)$_2$.2H$_2$O, the less soluble being the lævorotatory salt, α^{20}_{5461} −0·08° in 0·0053% solution, $[\alpha]^{20}_{5461} \sim -1500°$, were converted into the iodides by potassium iodide and crystallised to constant rotation, the active forms separating in the least soluble portions during crystallisation. The observed rotations in 0·004% solutions of [Os 3dipy]I$_2$.H$_2$O were +0·085° and −0·09°, hence $[\alpha]^{20}_{5461}$ are about +2100° and −2200° respectively. These figures correspond to molecular rotations of the order of ±21,000°. Although optical activity is manifested in mercury light (λ 5461), the solutions do not show rotation in Na_D light, the wave-length of which is close to an absorption maximum (see Figure) for these solutions. The complex osmium iodide clearly has an abnormal rotatory dispersion, and an investigation of this effect with this salt and the corresponding ruthenium, iron, and nickel complexes is at present being carried out by two of the authors (F. P. D. and E. C. G.). It should also be noted that oxidation of the optically active ion [Os 3dipy]$^{++}$ to the tervalent condition [Os 3dipy^{+++}] does not destroy the activity; moreover, the original activity is regained on reduction to the bivalent complex.

Absorption spectrum of Os(dipy)$_3$I$_2$.3H$_2$O ($c = 5{\cdot}5 \times 10^{-4}$M.).



The optical resolution of this bivalent osmium salt is the first recorded resolution of an osmium compound in any valency state.

Experimental.

Dichlorobis-2 : 2′-dipyridylosmium(III) *Chloride Trihydrate* (I).—An intimate mixture of potassium osmichloride (1 g.) and 2 : 2′-dipyridyl (5 g.) was heated and stirred at 260° for 1 hour. The cold dark brown solid was then extracted with benzene to remove excess of 2 : 2′-dipyridyl. The insoluble portion was leached with warm water until no more solid dissolved, and filtered from a brown microcrystalline residue which was not further studied. The aqueous filtrate was evaporated and cooled; red needles of the complex *chloride* then separated. After crystallisation from water this was air-dried (Found: Os, 28·7; Cl, 15·8; H$_2$O, 8·4. $C_{20}H_{14}N_4Cl_2Os.3H_2O$ requires Os, 28·7; Cl, 16·1; H$_2$O, 8·1%). A solution of this chloride in water or alcohol was decomposed by aqueous alkalis with separation of a black hydrated osmium oxide but was not altered by being heated with 2*N*-hydrochloric acid. With a large excess of ammonium (+)-tartrate, the chloride gave an unstable complex tartrate which gave only optically inactive preparations on regeneration of the chloride with ammonium chloride or hydrochloric acid. Aqueous potassium iodide and sodium nitrite gave crystalline sparingly soluble salts with strong solutions of the chloride.

Tris-2 : 2′-dipyridylosmium(II) *Chloride Hexahydrate* (II).—(*a*) The filtrate after separation of the red chloride (I) was made alkaline with 2*N*-sodium hydroxide, boiled for a few minutes to decompose tervalent salt, cooled, filtered from a black deposit of hydrated osmium oxide, acidified with hydrochloric acid, and evaporated to dryness. The green chloride was extracted with alcohol, the extract was evaporated, and the residue crystallised from a small quantity of water, to give lustrous dark green leaflets of the chloride (II).

(*b*) Potassium osmichloride or the tervalent salt (I) (0·5 g.), metallic osmium (0·1 g.), and 2 : 2′-dipyridyl were heated at 270° for 1 hour. After removal of excess of 2 : 2′-dipyridyl the residue was extracted with water, and the filtered solution was treated as described in (*a*).

(*c*) A solution of the complex iodide (see below) was triturated with an excess of freshly prepared silver chloride and then filtered, and the resulting dark green solution evaporated to dryness and dried over calcium chloride (Found: N, 10·1, 10·1; Cl, 8·8; Os, 23·0, 22·4; H$_2$O, 13·1. $C_{30}H_{24}N_6Cl_2Os.6H_2O$ requires N, 10·0; Cl, 8·5; Os, 22·7; H$_2$O, 13·0%). This *chloride* was easily soluble in water or alcohol but insoluble in ether or benzene.

Tris-2 : 2′-dipyridylosmium(II) *Bromide Trihydrate*.—This salt was obtained by (*a*) treating the chloride (II) with excess of freshly prepared silver oxide, filtering, and adding hydrobromic acid, (*b*) adding a concentrated solution of potassium bromide to a strong solution of the chloride (II), or (*c*) triturating the corresponding iodide with silver bromide, filtering, and evaporating the solution. This *bromide* which formed dark green hexagonal plates was dried over calcium chloride (Found: N, 9·8, 9·8, 9·9; Br, 18·3; Os, 21·5. $C_{30}H_{24}N_6Br_2Os.3H_2O$ requires N, 9·6; Br, 18·3; Os, 21·8%). It was slightly less soluble in water than was the corresponding chloride, but was otherwise similar.

Tris-2 : 2′-dipyridylosmium(II) *Iodide Trihydrate*.—Ammonium osmibromide (1·0 g.) and 2 : 2′-dipyridyl (2·0 g.) were mixed intimately and heated carefully in a test-tube until the base in the mixture melted and then became red. The test-tube was loosely stoppered and transferred to an oil-bath at 270—280° for 1 hour; a dark green, almost black product and an almost colourless liquid then remained.

The liquid consisting mainly of unchanged 2 : 2'-dipyridyl was decanted and the solid extracted with hot water (200 ml.). After filtration from traces of a dark insoluble material, the salts in solution were fractionally precipitated with aqueous potassium iodide. The first fraction consisted of a red salt which was not further studied, whereas the more soluble fractions consisted of nearly pure *tris*-2 : 2'-dipyridylosmium(II) iodide trihydrate which was washed with ice-water and crystallised from hot water with addition of potassium iodide. The complex *iodide*, which has also been made by adding potassium iodide to a solution of the corresponding chloride, formed almost black, lustrous monoclinic prisms and was dried over calcium chloride (Found: N, 8·8; I, 26·9, 26·3; Os, 19·5. $C_{30}H_{33}N_6I_2Os,3H_2O$ requires N, 8·8; I, 26·3; Os, 19·8%).

Tris-2 : 2'-*dipyridylosmium*(II) *Perchlorate Monohydrate*.—This *salt* separated, on addition of sodium perchlorate solution to a hot solution of the corresponding iodide, as a sparingly soluble microcrystalline deposit (Found: N, 9·6; Os, 21·4. $C_{30}H_{33}N_6O_9Cl_2Os,H_2O$ requires N, 9·6; Os, 21·7%).

Tris-2 : 2'-*dipyridylosmium*(II) *Hydroxide Octahydrate*.—This compound was prepared from the corresponding iodide and freshly prepared silver oxide. The mixture was filtered and evaporated to dryness over solid sodium hydroxide. The crystalline *base* was deliquescent and absorbed carbon dioxide from the air (Found: N, 10·0. $C_{30}H_{33}O_2N_6Os,8H_2O$ requires N, 10·1%). Solutions of this hydroxide liberate ammonia from ammonium salts and precipitate ferric and cupric hydroxides from solution.

Optical Activity of Bivalent Osmium Salts.—(1-Dm. tubes were used in all determinations of rotation.) (−)-*Tris*-2 : 2'-*dipyridylosmium*(II) *antimonyl* (+)-*tartrate dihydrate*. The racemic iodide [Os 3dipy]I_2,$3H_2O$ (2·0 g.) in hot water (150 ml.) was shaken with silver antimonyl (+)-tartrate (0·8 g.) for 10 minutes and the solution was then filtered. The filtrate was concentrated on a steam-bath until about half the salt in solution could be crystallised by cooling in ice. The crystals of the *tartrate* were separated and washed with small quantities of ice-cold alcohol to remove traces of the more soluble salts (Found: N, 6·6; Os, 15·0. $C_{34}H_{32}O_{10}N_6Sb_2Os,2H_2O$ requires N, 6·65; Os, 15·0%). A 0·0053% solution in water gave α^{20}_{5461} −0·08°.

(−)-*Tris*-2 : 2'-*dipyridylosmium*(II) *iodide trihydrate*. The foregoing antimonyl tartrate was dissolved in warm water and fractionally precipitated with potassium iodide solution. With the exception of the final fraction, which was slightly lævorotatory, all fractions were strongly active. These fractions were crystallised from water to constant rotation, racemate being left in the filtrates. The lævorotatory *iodide* formed flat micaceous plates (Found: N, 8·8; I, 26·4. $C_{30}H_{33}N_6I_2Os,3H_2O$ requires N, 8·7; I, 26·3%) which in 0·004% solution in water gave α^{20}_{5461} (mean) −0·09°.

(+)-*Tris*-2 : 2'-*dipyridylosmium*(II) *iodide trihydrate*. The filtrate from the preparation of the antimonyl tartrate was diluted with water to 120 ml., heated to 60°, and fractionally precipitated with aqueous potassium iodide. The less soluble fractions, which were strongly dextrorotatory, were crystallised several times from water with addition of potassium iodide and formed micaceous crystals of the dextrorotatory *iodide* (Found: N, 8·7; I, 26·0. $C_{30}H_{33}N_6I_2Os,3H_2O$ requires N, 8·7; I, 26·3%). A 0·004% solution in water gave α^{20}_{5461} (mean) +0·085°.

(+)-*Tris*-2 : 2'-*dipyridylosmium*(II) (+)-*tartrate trihydrate*. A solution of 0·3 g. of the chloride [Os 3dipy]Cl_2,$6H_2O$ in water (10 ml.) was cooled to 0° and treated with solid ammonium (+)-tartrate (3 g.); the tartrate of the dextrorotatory complex separated in lustrous plates. These were freed from liquid between filter paper and dried by being washed with acetone. The solid was dissolved in alcohol to separate ammonium tartrate, filtered, diluted with a few drops of water, and precipitated by addition of acetone. This *tartrate* was micro-crystalline (Found: N, 9·7; Os, 21·6. $C_{34}H_{32}O_{10}N_6Os,3H_2O$ requires N, 9·8; Os, 22·1%). A 0·005% solution gave α^{20}_{5461} +0·1°. A dextrorotatory iodide and bromide can be produced from this tartrate by addition of potassium bromide or iodide; lævorotatory salts can also be isolated from the mother-liquors after separation of the dextrorotatory tartrate.

Analyses.—The analyses of the compounds for carbon and hydrogen were unsatisfactory owing to deposition of osmium in the absorption tubes. Halogen was determined by the distillation method (Dwyer and Nyholm, *J. Proc. Roy. Soc., New South Wales*, 1941, **75**, 127), nitrogen by the combustion method (Dumas), and osmium by a colorimetric procedure which will be recorded elsewhere (Dwyer and Gibson).

The work, carried out at the Chemical Research Laboratory (1935—1936), formed part of the programme of the Chemistry Research Board and is published by permission of the Director. The authors are indebted to Dr. F. Lions for 2 : 2'-dipyridyl and one of them (E. C. G.) thanks the Research Committee of the University of Sydney for a Research Assistantship.

Chemical Research Laboratory, Teddington, Middlesex.
University of Sydney, Sydney, N.S.W., Australia. [*Received, November 21st*, 1949.]

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195. *Diterpenes. Part III. The Diterpenes from* Podocarpus ferrugineus.

By Lindsay H. Briggs, R. W. Cawley, J. A. Loe, and W. I. Taylor.

The diterpene fraction of the essential oil of *Podocarpus ferrugineus* has been found to contain (+)-phyllocladene, (+)-kaurene, and a new dextrorotatory isomer, m. p. 59—60°. A re-examination of crude "mirene" and "mirene hydrochloride" (Hosking and Short, *Rec. Trav. chim.*, 1928, **47**, 834) showed them to contain phyllocladene and kaurene hydrochloride, respectively. It is evident that "mirene" was not homogeneous, and was probably impure isophyllocladene. The name mirene has been transferred to the new isomer.

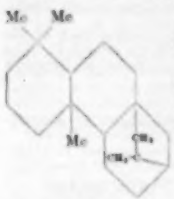
From the essential oil of *Podocarpus ferrugineus* ("miro") Hosking and Short (*Rec. Trav. chim.*, 1928, **47**, 834) isolated an apparently new diterpene, mirene, m. p. 102—104°, $[\alpha]^{15}_{5461}$

+27·15°,* forming a monohydrochloride, m. p. 97—98°, from which the hydrocarbon was regenerated on treatment with alcoholic potassium hyroxide, and a dihydro-derivative, m. p. 73—74° (Hosking, *Rec. Trav. chim.*, 1930, **49**, 1036). Following an observation by one of us (Briggs, *Proc. Aust. New Zealand Assoc. Adv. Sci.*, 1937, **23**, 45) that the m. p. of dihydromirene was the same as that of α-dihydrophyllocladene, suggesting a relationship between mirene and phyllocladene, samples of mirene hydrochloride and dihydromirene were submitted by Dr. J. R. Hosking to Mr. C. W. Brandt with the suggestion that they would prove identical with phyllocladene hydrochloride and α-dihydrophyllocladene, respectively. No depressions in m. p. were observed (Brandt, *New Zealand J. Sci. Tech.*, 1938, **20**, 8B) thus confirming the suggestion. Brandt also obtained a hydrocarbon, m. p. 103°, by treating the hydrochloride with alcoholic potassium hydroxide, which did not depress the m. p. of *iso*phyllocladene. His regenerated hydrocarbon was reported as lævorotatory, however, whereas *iso*phyllocladene is dextrorotatory, and from our experience in the kaurene series a strong depression should have been observed with the enantiomorphs. Brandt, however, in a private communication, has informed us that the rotation of his regenerated hydrocarbon was done on a micro-scale, and he would not insist that the rotation was negative under the experimental conditions.

It would appear therefore that mirene is an impure form of *iso*phyllocladene, the purest specimen of which has m. p. 112° (Briggs and Sutherland, *J. Org. Chem.*, 1942, **7**, 397).

With the kind permission of the late Dr. J. R. Hosking we have continued the investigation of the diterpene fraction of the essential oil of this species. In contrast with the results of Hosking and Short we have isolated, by fractional crystallisation, three diterpenes, (+)-phyllocladene, identified by mixed m. p. and Debye–Scherer patterns, (+)-kaurene, identified by Debye–Scherer patterns and conversion into (+)-*iso*kaurene, and a new diterpene, m. p. 59—60°, $[\alpha]_D^{20}$ +43·8° (monohydrochloride, m. p. 82°, and dihydro-derivative, m. p. 63—64°). Since the original mirene from this oil has been shown to be *iso*phyllocladene, we have transferred the name mirene to the new isomer. Like rimuene (McDowall and Finlay, *J. Soc. Chem. Ind.*, 1925, **44**, 427), phyllocladene (Aitken, *J. Soc. Chem. Ind.*, 1928, **47**, 223), and cupressene (Briggs and Sutherland, *loc. cit.*), mirene is isomerised by glacial acetic acid into *iso*phyllocladene. Mirene gives a strong m. p. depression when mixed with rimuene and its Debye–Scherer pattern shows that it is neither identical with nor an enantiomorph of α-cryptomerene from *Cryptomeria japonica* (Uchida, *Bull. Forest Expt. Stat. Meguro, Tokyo*, 1915, Reprint) for a sample of which we are greatly indebted to Professor Uchida.

Through the courtesy of Professor L. Ruzicka, to whom we are greatly indebted, we have been able to re-examine some of the original material of Hosking and Short. A sample of "crude mirene," m. p. 60—70°, on crystallisation afforded (+)-phyllocladene, identified through mixed m. p., rotation, and conversion into *iso*phyllocladene and α-dihydrophilloc1adene. On the other hand, a sample of "mirene hydrochloride," m. p. 94°, yielded (+)-kaurene hydrochloride, m. p. 116°, on crystallisation, identified through its m. p., rotation, and conversion into (+)-*iso*kaurene, undepressed in m. p. by an authentic specimen. With the small amount of material at our disposal it was not possible to examine the mother liquors for mirene.



Brandt [already reported by one of us (Briggs, *Proc. Roy. Soc. New South Wales*, 1947, **80**, 154)] has adduced evidence for the inset structure for phyllocladene. Four stable geometrical isomerides of this structure may occur, each in (+)- and (−)-forms, and it would appear that a number of naturally occurring diterpenes are stereoisomers of the same general pattern.

Kaurene is isomerised by boiling glacial acetic acid into *iso*kaurene but with boiling alcoholic sulphuric acid it is converted into the γ-isomer, m. p. 196—198°, reported by Nishida and Uoda (*Bull. Agric. Soc. Japan*, 1930, **1**, Nos. 1—3), under conditions which left *iso*phyllocladene unchanged. *iso*Kaurene does not depress the m. p. of kaurene and forms a eutectic containing 60% kaurene and 40% *iso*kaurene.

Experimental.

The leaves and terminal branchlets of *Podocarpus ferrugineus* (140 lb.), collected at Mangapehi in June through the courtesy of Mr. G. R. Hammond, State Forest Service, to whom we are greatly indebted, produced 95 g. (0·15% yield) of a pale yellow oil on steam distillation. The oil was distilled

* The lævorotation of mirene reported by one of us (Briggs, *Proc. Aust. New Zealand Assoc. Adv. Sci.*, 1937, **23**, 45) and Brandt (*New Zealand J. Sci. Tech.*, 1938, **20**, 8B) is an error.

in a Bower and Cooke type of column (*Ind. Eng. Chem. Anal.*, 1943, **15**, 290), the lower terpene fractions at 20 mm. and the higher fractions at 3·5 mm., the bath temperature not rising above 215° at any stage. No attempt was made to separate the constituents below the diterpene fraction. The following major fractions were obtained :

Fraction.	B. p.	n_D^{25}.	Wt., g.
I	<47°/20 mm.	1·464	37·8
II	45—125/3·5 mm.	1·464 ~ 1·492	11·3
III	130—160/3·5 mm.	1·514	13·0

The residual brown oil (45 g.) solidified (m. p. *ca.* 40—45°) and was investigated for diterpenes.

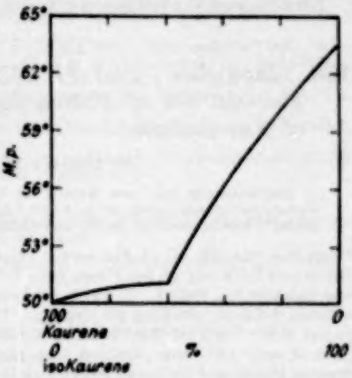
Separation of this material into three constituents was only achieved by a long series of systematic fractional crystallisations from ethyl acetate and both alcohol and absolute alcohol. Coloured material which hindered crystallisation was removed at certain stages by chromatographing solutions in light petroleum through a 20 × 1 cm. column of alumina. By this means the following constituents were obtained.

(+)-*Phyllocladene*.—The small amount of pure material (<400 mg.) had m. p. and mixed m. p. with authentic (+)-phyllocladene (from *Araucaria excelsa*) 96°, whilst the Debye–Scherer diagrams were identical.

(+)-*Kaurene*.—Only 1·1 g. were obtained in a pure state; it had m. p. 49° and $[\alpha]_D^{20}$ +101° (*l* = 1; *c*, 1·5 in chloroform). It gave a m. p. depression when mixed with (−)-kaurene (from *Agathis australis*) but the Debye–Scherer diagrams were identical.

A sample of the diterpene isolated from the essential oil of *Podocarpus spicatus* by Butler and Holloway (*J. Soc. Chem. Ind.*, 1939, **58**, 223) was kindly sent to us for comparison. It proved to be lævorotatory whilst the Debye–Scherer diagram indicated that it was mixture of kaurene and *iso*kaurene.

The melting-point diagram for mixtures of kaurene and *iso*kaurene, showing a eutectic at 40% kaurene + 60% *iso*kaurene, is given in the figure.



Isomerisation of Kaurene.—(a) *With glacial acetic acid*. (−)-Kaurene (100 mg., from *Agathis australis*), dissolved in glacial acetic acid (6 c.c.), was gently heated under reflux for 1½ hours. The product separating on cooling, after repeated crystallisation from alcohol, formed plates, m. p. and mixed m. p. with (−)-*iso*kaurene 64°. The enantiomorph, of the same m. p., was similarly obtained from (+)-kaurene.

(b) *With alcoholic sulphuric acid*. (−)-Kaurene (100 mg.), dissolved in alcohol (9 c.c.) and concentrated sulphuric acid (3 drops), was heated under reflux for 6½ hours. The material separating on cooling was crystallised repeatedly from alcohol and then formed prismatic needles, m. p. 196—198° [Found : *M* (micro-Rast), 266, 268. Calc. for $C_{20}H_{32}$: *M*, 272].

Mirene.—This is apparently the diterpene occurring in the greatest amount, and 3·2 g. of pure material were obtained. No alteration in m. p. could be achieved by repeated crystallisation from ethyl acetate or alcohol from which *mirene* separated in rectangular plates, or in any fraction after chromatographing the solution through a 20-cm. column of alumina (Brockmann, grade I). The Debye–Scherer diagram also indicated homogeneity and proved that it was not identical with cryptomerene of similar m. p. (Found : C, 88·5; H, 12·3. $C_{20}H_{32}$ requires C, 88·2; H, 11·8%), $[\alpha]_D^{20}$ +43·8° (*l* = 1, *c*, 4·1 in chloroform).

Isomerisation of mirene to iso*phyllocladene*. Mirene (100 mg.) was heated in glacial acetic acid solution (10 c.c.) for 6 hours. The solid separating on cooling, after recrystallisation from alcohol (charcoal), formed needles, m. p. 110°, undepressed by *iso*phyllocladene, $[\alpha]_D^{20}$ +23·08° (*l* = 0·25, *c* = 0·2 in chloroform). Briggs (*J.*, 1937, 79) records $[\alpha]_D^{17}$ +23·4° for *iso*phyllocladene.

Dihydromirene. A solution of mirene (100 mg.) in glacial acetic acid (15 c.c.) was hydrogenated at 34 lb. per sq. in. pressure for 16 hours in the presence of palladised charcoal (100 mg.). After concentration of the filtered solution, *dihydromirene* separated in plates which, after repeated crystallisation from glacial acetic acid, had m. p. 63—64° (Found : C, 87·4; H, 12·7. $C_{20}H_{34}$ requires C, 87·6; H, 12·4%).

Mirene hydrochloride. Dry hydrogen chloride was passed through a solution of mirene (100 mg.) in glacial acetic acid (2 c.c.) and dry ether (0·5 c.c.) cooled in ice. The colourless solid which formed was washed with glacial acetic acid and ethyl acetate and recrystallised from ethyl acetate to a constant m. p. The *hydrochloride* had m. p. 82°, $[\alpha]_D^{20}$ +59·9° (*l* = 1; *c*, 0·4 in chloroform) (Found : Cl, 12·0. $C_{20}H_{33}$.HCl requires Cl, 11·5%).

Re-examination of Hosking and Short's Material.—Isolation of phyllocladene. A sample (450 mg.) of Hosking and Short's material, labelled "crude mirene," had m. p. 60—70°. On crystallisation from absolute alcohol this formed plates, m. p. 91—93° (yield, 400 mg.), raised by further crystallisation to m. p. 95—96° (yield, 300 mg.) and two further crystallisations to a constant m. p. 96—97°, undepressed by authentic (+)-phyllocladene, $[\alpha]_D^{20}$ +15·5° ± 2° (*l* = 1; *c*, 2·27 in chloroform).

The purified material (40 mg.) was heated under reflux with alcoholic sulphuric acid (2 c.c.; 10% solution) for ½ hour. The plates separating on cooling, after recrystallisation from absolute alcohol, formed needles, m. p. 111—112°, undepressed by authentic (+)-*iso*phyllocladene, $[\alpha]_D^{20}$ +23·6° ± 2° (*l* = 1; *c*, 1·92 in chloroform).

The purified material (60 mg.) was hydrogenated in glacial acetic acid solution in the presence of platinum oxide. Concentration of the filtered solution afforded needles, which, after recrystallisation from the same solvent, had m. p. 70—71°, undepressed by an authentic sample of (+)-α-dihydrophyllocladene (Found: C, 87·1; H, 12·4. Calc. for $C_{20}H_{34}$: C, 87·5; H, 12·5%). $[\alpha]_D^{19}$ +21° ± 2° (*l* = 1; *c*, 1·12 in chloroform).

Isolation of kaurene derivatives. A sample of Hosking and Short's "mirene hydrochloride" had m. p. 94°, raised to 115—116° by a single crystallisation from ethyl acetate and to 116° by a further crystallisation (Found: C, 77·7; H, 10·9. Calc. for $C_{20}H_{35}Cl$: C, 77·8; H, 10·8%). $[\alpha]_D^{19}$ +38·5° ± 1° (*l* = 1; *c*, 2·0 in chloroform). In Part I (*J.*, 1948, 1888) values of m. p. 114—115° and $[\alpha]_D^{20}$ −40·0° are recorded for (−)-kaurene hydrochloride.

The hydrochloride (100 mg.) was heated under reflux with alcoholic sodium hydroxide (5 c.c.; 3% solution) for 3 hours. After addition of water, the diterpene was extracted with chloroform and repeatedly crystallised from absolute alcohol, from which it separated in plates or needles, m. p. 64—65°, undepressed by authentic (+)-*iso*kaurene (Found: C, 88·0; H, 11·7. Calc. for $C_{20}H_{32}$: C, 88·2; H, 11·8%). $[\alpha]_D^{19}$ +31° ± 2° (*l* = 1; *c*, 1·79 in chloroform). In Part I (*loc. cit.*) a value of $[\alpha]_D^{20}$ −25·9° is recorded for (−)-*iso*kaurene.

The analyses are by Drs. Weiler and Strauss, Oxford, Mr. Manser, Zürich, and Mr. Seelye of this department.

We are indebted to the Chemical Society, the Australian and New Zealand Association for the Advancement of Science, and the Royal Society of New Zealand for grants, and to Mr. L. D. Calvert for the *X*-ray powder photographs. One of us (W. I. T.) is grateful for a National Research Scholarship.

AUCKLAND, UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND.
EIDG. TECHNISCHEN HOCHSCHULE, ZÜRICH, SWITZERLAND. [*Received, November 24th*, 1949.]

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196. *Diterpenes. Part IV. The Isolation of Phyllocladene from the Essential Oil of* Podocarpus spicatus *Grown in the North Island of New Zealand.*

By LINDSAY H. BRIGGS and J. A. LOE.

Phyllocladene has been isolated as the only solid diterpene from the essential oil of *Podocarpus spicatus* grown in the North Island of New Zealand, whereas that grown in the South Island yields kaurene (cf. Butler and Holloway, *J. Soc. Chem. Ind.*, 1939, **58**, 223).

FROM the essential oil of *Podocarpus spicatus* growing in the South Island of New Zealand Butler and Holloway (*J. Soc. Chem. Ind.*, 1939, **58**, 223) isolated a diterpene which they suggested was kaurene [cf. Part I (*J.*, 1948, 1888) for the identification of podocarpene with kaurene] without definitely claiming its identity. From the evidence submitted in Part III (preceding paper) it is clear that they isolated the lævo-isomer. Seeking a better source of kaurene [a yield of only 1·2% was obtained from the essential oil of *Agathis australis* (Part I, *loc. cit.*) whereas Butler and Holloway record a yield of 25% from the oil of *Podocarpus spicatus*], we have examined the essential oil of *P. spicatus* grown in the centre of the North Island of New Zealand. Although a thorough search, by careful fractionation followed by chromatography, was made for different diterpenes, particularly kaurene, the only diterpene isolated was phyllocladene in very small yield.

Wide variation in the percentage of constituents and also in the type of compounds present in species of plants, morphologically indistinguishable, has frequently been observed in the Australian flora but this is the first record from New Zealand.

The essential oil of *Podocarpus totara* contains rimuene and possibly a liquid diterpene, totarene (Aitken, *J. Soc. Chem. Ind.*, 1929, **48**, 344T; Beath, *ibid.*, 1933, **52**, 338T). The isolation of phyllocladene from the leaf-oil of "*P. hallii*," considered by botanists to be a variety of *P. totara* and not a separate species led one of us (Briggs, *Proc. Roy. Soc. New Zealand*, 1941, **70**, 173) to the suggestion that this fact would support the classification of *P. hallii* as a true species and not a variety. The above evidence from *P. spicatus* weakens the case for such a suggestion.

An unusual constituent, a liquid *olefin*, $[CH_2]_n$, b.p. 130—135°/0·01 mm., was isolated from the diterpene portion of the oil.

EXPERIMENTAL.

The leaves and terminal branchlets of *Podocarpus spicatus* (832 lbs.) collected from the Pureora Forest, Mangapehi, through the courtesy of Mr. G. R. Hammond, State Forest Service, to whom we are greatly indebted, produced, on steam distillation for 16—18 hours, 477 g. (0·13% yield) of pale yellow oil. The oil was then distilled through a column of the type described by Dostrovsky and Hughes (*Nature*, 1946, **158**, 164), the terpene fraction (279 g.) at 10 mm. and the oxygenated terpenes and sesquiterpene fraction

(89 g.) at 5 mm. The temperature of the still-pot did not exceed 140° at any stage. The residual oil was transferred to a modified Craig column (*Ind. Eng. Chem. Anal.*, 1937, **9**, 441), 20 cm. long, without condenser and with a side arm dipping into a series of receivers, and was distilled at 0·01 mm. The first yellowish-green fraction (33·8 g.), b. p. 66—97°/0·01 mm., n_D^{20} 1·5056 ~ 1·5057, consisted of sesquiterpene alcohols whilst the remaining fractions: *A*, greenish-blue (3·82 g.), b. p. 111—122°/0·01 mm., n_D^{20} 1·5059; *B*, greenish blue (3·52 g.), b. p. 122—129°/0·01 mm., n_D^{20} 1·5102; *C*, blue (8·95 g.), b. p. 129—145°/0·01 mm., n_D^{20} 1·5173; *D*, blue (2·90 g.), b. p. 130—140°/0·01 mm., n_D^{20} 1·5177; and the residue (24·5 g.) were investigated for diterpenes.

Fractions *A* and *B* were dissolved in dry light petroleum (10 c.c.), chromatographed on a 18 × 1·5 cm. column of alumina (Brockmann, grade I), and eluted with light petroleum and finally with light petroleum containing 1% methyl alcohol. Six fractions, each of *ca.* 10 c.c., were collected in each case, and the solvent was removed and the residual oils were kept dry in the refrigerator. No solid separated from any of these fractions.

A part of fraction *C* (1·89 g.) was similarly treated and gave the following fractions (all colourless):

Fraction	*C*1	*C*2	*C*3	*C*4	*C*5—*C*10
n_D^{20}	1·5100	1·5158	1·5174	1·5205	—
Weight (g.)	0·01	0·81	0·51	0·30	0·03

From *C*2 a solid separated (12 mg.) which, after recrystallisation from alcohol, had m. p. 95°, undepressed by a specimen of phyllocladene. A trial experiment showed that phyllocladene was not isomerised on chromatography as above.

Fraction *C*4 was distilled in a Craig micro-column and gave an oil, b. p. 130—135°/0·01 mm., n_D^{18} 1·5202, d_4^{18} 0·9718 (determined in a micro-pyknometer similar to that described by Clemo and McQuillen, *J.*, 1935, 1220), $[\alpha]_D^{18}$ + 39·73° (*l* = 1, *c* = 0·8 in chloroform) (Found: C, 85·9; H, 14·2. $(CH_2)_n$ requires C, 85·7; H, 14·3%). The *hydrocarbon* decolorised a solution of bromine in chloroform and gave a brown coloration with tetranitromethane.

From the main bulk of fraction *C* a colourless solid separated which, after recrystallisation from alcohol, had $[\alpha]_D^{20}$ + 14·99° (*l* = 1, *c* = 2·1 in chloroform) and m. p. 96°, undepressed by phyllocladene. Briggs (*J.*, 1937, 79) records $[\alpha]_D^{20}$ + 15·8° for phyllocladene. The material, after isomerisation with sulphuric acid in alcoholic solution (Briggs, *loc. cit.*) and crystallisation from methyl alcohol, had m. p. 109—110°, undepressed by a specimen of isophyllocladene.

The solid separating from fraction *D* was also proved to be phyllocladene by mixed m. p. and rotation, $[\alpha]_D^{20}$ + 15·62° (*l* = 1, *c* = 0·3 in chloroform).

The residue was only partly soluble in hot alcohol from which solution there separated on storage 2 g. of crystalline material which was proved to be phyllocladene by mixed m. p.

The analysis is by Mr. Seelye of this department.

We are indebted to the Chemical Society, the Royal Society of New Zealand, and the Australian and New Zealand Association for the Advancement of Science for grants.

AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, November 24th*, 1949.]

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197. *The Preparation of a Series of* (±)-n-*Eicosanols and* n-*Eicosanones.*

By VIVIENNE R. CHURCHWARD, N. A. GIBSON, R. J. MEAKINS, and JOAN W. MULLEY.

The preparation and properties of the (±)-n-eicosanols ($C_{20}H_{41}OH$) and n-eicosanones ($C_{20}H_{40}O$) having the polar groups in the 2-, 4-, 6-, 8-, and the 10-position are described.

IN the course of a programme of research into the dielectric properties of long-chain alcohols (Meakins and Sack, *Nature*, 1949, **164**, 798) and ketones (Meakins, *Nature*, 1948, **162**, 994; 1949, **163**, 840) it was desired to determine the effect of varying the position of the polar group in a normal paraffin chain. Eicos-2-,-4-,-6-,-8- and -10-ol and -one now described were prepared for that purpose. Of these compounds, only the n-eicosan-2-ol and n-eicosan-2-one have been reported previously (Pangborn and Anderson, *J. Amer. Chem. Soc.*, 1936, **58**, 10; Morgan and Holmes, *J. Soc. Chem. Ind.*, 1925, **44**, 108; Stenhagen and Stenhagen, *Arkiv Kemi., Mineral., Geol.*, 1945, **18**, *A*, No. 19).

The n-eicosanols were obtained by the Grignard reaction between alkylmagnesium iodides and the appropriate aldehydes, the product being separated from the hydrocarbon by-product by vacuum distillation, recrystallisation, or adsorption on alumina, according to chain-length. The yields varied from 20 to 55%, the higher yields being obtained with the alkyl halides of shorter chain-length. Pure, fresh-cut magnesium (99·95%) was used throughout.

EXPERIMENTAL.

(All m. p.s are uncorrected.)

(±)-n-*Eicosan*-2-ol.—The Grignard reagent was prepared from magnesium (9·5 g.), octadecyl iodide (119 g.), and ether (350 ml.), the mixture being heated under reflux during the addition of the iodide and

for a further one hour. After the solution had cooled to room temperature, a solution of acetaldehyde (14 g.) in dry ether (15 ml.) was added slowly, with stirring. After being heated under reflux for a further 2 hours, the Grignard complex was decomposed with water (50 ml.), and 5*N*-hydrochloric acid (200 ml.) was added to dissolve the excess of magnesium. The ethereal layer was then separated, filtered to remove n-hexatriacontane, and washed with water, dilute sodium thiosulphate solution, and again several times with water, and dried (Na_2SO_4), and the ether distilled off.

The residual solid was dissolved in benzene and chromatographed on a column of alumina (1,100 g., 5 cm. in diameter. Elution with benzene (1 l.) removed the hydrocarbon by-products and the crude (±)-n-eicosan-2-ol was then obtained by elution with ether. Recrystallisation from light petroleum gave a product (11·7 g.) in the form of well-defined crystalline plates, m. p. 59—60°. A portion of this was distilled under vacuum and the second of three fractions (b. p. 208—212°/7 mm.), having the smallest melting-point range, was recrystallised from alcohol. This gave (±)-n-eicosan-2-ol as a microcrystalline powder (well-defined plates from benzene), m. p. 58·5—59·0° (Lit., m. p. 52·0—52·7° for the (±)-compound; m. p. 62—63° for the (+)-form) (Found: C, 80·5, 80·3; H, 13·9, 13·8. Calc. for $C_{20}H_{42}O$: C, 80·5%; H, 14·1%).

(±)-n-*Eicosan-4-ol*.—This was similarly prepared from magnesium (2·5 g.) in dry ether (30 ml.), cetyl iodide (30 g.) in dry ether (50 ml.), and butyraldehyde (6·1 g.). The material obtained by elution of the chromatograph column with ether was recrystallised from light petroleum (b. p. 60—80°) then benzene, giving microcrystalline needles (7·7 g.), m. p. 54·0—54·5°. A portion of this product was distilled under vacuum and the second (b. p. 190—192°/3 mm.) of three fractions recrystallised from alcohol, giving (±)-n-*eicosan-4-ol* as microcrystalline needles (poorly defined), m. p. 55·0—55·3° (Found: C, 80·5, 80·5; H, 13·8, 13·9. $C_{20}H_{42}O$ requires C, 80·5; H, 14·1%).

(±)-n-*Eicosan-6-ol*.—This was prepared from magnesium (9·0 g.) in dry ether (200 ml.), tetradecyl iodide (160 g.) in dry ether (200 ml.), and hexanal (25·8 g.). The n-octacosane by-product was not precipitated, and was therefore contained in the solid mixture obtained by evaporation of the ether solution. This mixture was dissolved in light petroleum (b. p. 60—80°) and chromatographed on a column of alumina (1,500 g.), 5 cm. in diameter. Elution with light petroleum eliminated the hydrocarbons, and the eicosanol was then obtained by elution with benzene. Recrystallisation from light petroleum gave a product (24·1 g.), m. p. 55—57°, which was vacuum-distilled. The second fraction (b. p. 189°/2·7 mm.) was recrystallised from alcohol, giving (±)-n-*eicosan-6-ol* as a microcrystalline powder (needles from benzene), m. p. 57·7—57·8° (Found: C, 80·5, 80·5; H, 13·9, 13·8%).

(±)-n-*Eicosan-8-ol*.—The scale of the preparation was the same as that described for (±)-n-eicosan-6-ol. The mixture obtained from the ether solution was partly distilled under a vacuum to remove n-dodecane and the residue recrystallised from light petroleum (900 ml.; b. p. 60—80°), giving a product (62 g.), m. p. 57—59°. A portion of this was distilled under a vacuum and the second (b. p. 192°/3 mm.) of three fractions recrystallised from alcohol, giving (±)-n-*eicosan-8-ol* as microcrystalline plates (short needles from benzene), m. p. 57·7—57·9° (Found: C, 80·6, 80·4; H, 14·1, 13·8%).

(±)-n-*Eicosan-10-ol*.—The reaction product from the ether layer was recrystallised from light petroleum (500 ml.; b. p. 60—80°), giving a product, m. p. 62·5—64°. A portion of this was distilled under a vacuum and the second (b. p. 214°/7 mm.) of three fractions recrystallised from alcohol, giving (±)-n-*eicosan-10-ol* as microcrystalline plates (well-defined needles from benzene), m. p. 65·3—65·6° (Found: C, 80·5, 80·5; H, 14·0, 13·8%).

The Preparation of the n-*Eicosanones*.—A solution of the n-eicosanol (5 g.) in benzene (250 ml.) was added to a solution of sodium dichromate (7 g.) in acetic acid (5 ml.), sulphuric acid (9 ml.), and water (30 ml.), and the mixture shaken mechanically for 6 hours. The aqueous layer was removed, and the benzene layer washed with water, 0·5*N*-potassium hydroxide, and again several times with distilled water. The n-eicosanone was then obtained by evaporation of the benzene solution, and recrystallisation of the product twice from alcohol. The yield of pure product was, in each case, about 90%.

n-Eicosan-2-one formed crystalline flakes, m. p. 59·3—59·7° (lit. m. p. 58°) (Found: C, 81·0, 80·7; H, 13·5, 13·6; O, 5·6. Calc. for $C_{20}H_{40}O$: C, 81·1%; H, 13·5; O, 5·4%). 2 : 4-Dinitrophenylhydrazone: orange-yellow crystalline plates, m. p. 94·5—94·8°.

n-*Eicosan-4-one* was obtained as crystalline flakes, m. p. 54·0—54·5° (Found: C, 80·7, 80·8; H, 13·8, 14·0; O, 5·6%). 2 : 4-Dinitrophenylhydrazone: brick-red microcrystalline plates, m. p. 70·1—70·4°.

n-*Eicosan-6-one* formed crystalline flakes, m. p. 53·8—54·1° (Found: C, 81·4, 81·3; H, 13·8, 14·0; O, 5·6%). 2 : 4-Dinitrophenylhydrazone: yellow powder, m.p. 40·4—47·4°.

n-*Eicosan-8-one* formed crystalline flakes, m. p. 53·2—53·5° (Found: C, 81·0, 81·3; H, 13·8, 13·6; O, 5·7%). 2 : 4-Dinitrophenylhydrazone: yellow needles, m. p. 29·6—30·0°.

n-*Eicosan-10-one* was obtained as crystalline flakes, m. p. 53·7—54·0° (Found: C, 80·9, 81·0; H, 13·3, 13·4; O, 5·6%). The 2 : 4-dinitrophenylhydrazone was a yellow liquid at room temperature.

The work described formed part of the programme of the Division of Electrotechnology, Commonwealth Scientific and Industrial Research Organisation.

The authors thank Mr. R. Bradbury for the microanalyses.

Division of Electrotechnology,
Commonwealth Scientific and Industrial Research Organisation,
Australia.

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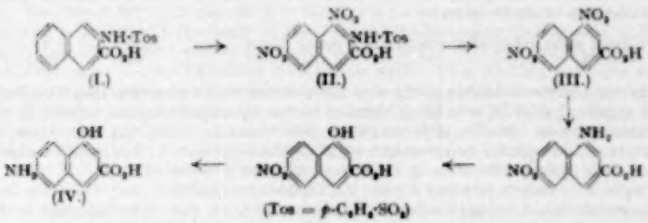
198. *Aminohydroxynaphthoic Acids. Part II. Attempted Synthesis of 7-Amino-4-hydroxy-2-naphthoic Acid ("Carboxy J-Acid") from 3-Amino-2-naphthoic Acid.*

By W. F. Beech and N. Legg.

A number of nitro- and bromo-derivatives of 3-amino-2-naphthoic acid have been prepared in an attempt to find a suitable route to 7-amino-4-hydroxy-2-naphthoic acid (IV). Poor yields of two suitable intermediates, 4 : 7-dinitro- and 4 : 7-dibromo-2-naphthoic acid, prevented their attempted conversion into the aminohydroxynaphthoic acid.

In Part I (*J.*, 1949, 1887), which described a synthesis of 6-amino-4-hydroxy-2-naphthoic acid ("carboxy γ-acid"), the reasons for undertaking this work were given, and as J-acid (7-amino-4-naphthol-2-sulphonic acid) is one of the most important dyestuffs intermediates of its class it was desirable to synthesise its carboxy-analogue.

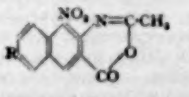
Since toluene-*p*-sulphon-2-naphthalide can be nitrated to give the 1 : 6-dinitro-derivative (Morgan and Micklethwait, *J.*, 1912, **101**, 148), it was hoped that 3-toluene-*p*-sulphonamido-2-naphthoic acid (I) would similarly give a dinitro-derivative (II) which could be converted into "carboxy J-acid" by the following route :



3-Amino-2-naphthoic acid reacted with toluene-*p*-sulphonyl chloride to give (I). This was nitrated in glacial acetic acid at 55° to give the 4-nitro-derivative, which on hydrolysis in concentrated sulphuric acid gave 4-nitro-3-amino-2-naphthoic acid, previously prepared by Cross and Drew (*J.*, 1949, 1532) by the nitration of 3-acetamido-2-naphthoic acid. 4-Nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid on further nitration in acetic acid gave a small yield of 4 : 7-dinitro-3-toluene-*p*-sulphonamido-2-naphthoic acid (II), which after hydrolysis to 4 : 7-dinitro-3-amino-2-naphthoic acid was deaminated to give 4 : 7-dinitro-2-naphthoic acid (III). This was decarboxylated to 1 : 6-dinitronaphthalene thus orientating the nitro-groups.

As the yield of (II) was too low to permit a continuation of this synthesis of (IV) the nitration of 4-nitro-3-acetamido-2-naphthoic acid was investigated, but all attempts to obtain a dinitro-compound failed, the mononitro-derivative being recovered unchanged.

A sample of 4 : 7-dinitro-3-acetamido-2-naphthoic acid was prepared by acetylating 4 : 7-dinitro-3-amino-2-naphthoic acid with acetic anhydride and concentrated sulphuric acid. The use of acetic anhydride alone gave the anhydro-derivative (V) which was converted into the acetyl compound by hydrolysis with water.



(V; R = NO_2)
(VI; R = H)

4-Nitro-3-amino-2-naphthoic acid reacted similarly with acetic anhydride to give (VI), whilst the addition of concentrated sulphuric acid gave an inseparable mixture of the acetyl compound and the anhydro-derivative. Hydrolysis of this mixture with water gave 4-nitro-3-acetamido-2-naphthoic acid. 3-Amino-2-naphthoic acid, under similar conditions, gave 3-acetamido-2-naphthoic acid. From these results it is obvious that the nitro-group favours ring closure, by dehydration, of the acetyl compound when acetic anhydride is used. Addition

of concentrated sulphuric acid partially prevents this anhydro-formation in the 4-nitro-derivative, and completely prevents it in the 4 : 7-dinitro-derivative.

According to Baker ("Tautomerism," 1934, p. 136) the amide grouping can exist in the tautomeric forms shown above. From the evidence obtained, it seems probable that 3-acetamido-2-naphthoic acid, in the presence of acetic anhydride, normally exists in the keto-form, but the presence of the 4-nitro-group favours the formation of the enol by withdrawing electrons from the side chain, the anhydro-compound being then formed by simple dehydration of the two hydroxyl groups. Addition of concentrated sulphuric acid represses the formation of the *aci*-nitro-form so that the amide remains in the keto-form and hence ring closure does not occur.

Since a route to "carboxy J-acid" using 4 : 7-dinitro-2-naphthoic acid (III) was impossible, practically, owing to the low yield at the second nitration stage, the bromination of 4-nitro-3-acetamido-2-naphthoic acid was investigated. The latter reacted with bromine in boiling glacial acetic acid to give 7-bromo-4-nitro-3-acetamido-2-naphthoic acid (VII), the orientation of which is discussed later.

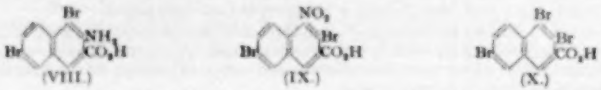
It was found that the yield of (VII) fell if the reaction mixture was heated under reflux after the addition of the bromine:

Time of heating under reflux after addition of bromine, hours	0	1	2½
Yield of (VII), %	63·5	53·7	45·6

As the only other isolatable product of the reaction was 4-nitro-3-amino-2-naphthoic acid it would appear that (VII) was being reduced by the hydrogen bromide formed in the initial bromination reaction. Fries and Schimmelschmidt (*Annalen*, 1930, **484**, 245) found that the bromination of 2-naphthol is reversible in that 1-bromo- and 1 : 6-dibromo-2-naphthol on treatment with hydrogen bromide in acetic acid afforded 2-naphthol.

Attempts to convert 7-bromo-4-nitro-3-acetamido-2-naphthoic acid (VII) by hydrolysis and deamination into 7-bromo-4-nitro-2-naphthoic acid failed as no method could be found for removing the acetyl group without replacing either the nitro- or the bromo-group, the former by alkaline reagents and the latter by acids.

The acetamido-naphthoic acid (VII) reacted with aqueous sodium carbonate to give a compound of unknown structure containing bromine, and with diethylamine to give 7-bromo-3-amino-4-diethylamino-2-naphthoic acid. With ethanol and hydrochloric acid (VII) gave 4-nitro-3-amino-7-ethoxy-2-naphthoic acid and 4-nitro-3-amino-2-naphthoic acid. The formation of the latter compound is unusual and cannot readily be explained. Although (VII) had been reduced to 4-nitro-3-amino-2-naphthoic acid by the action of hydrogen bromide in acetic acid it was thought that aqueous hydrobromic acid would act solely as a deacetylating reagent. The use of 48% hydrobromic acid gave a mixture of 4 : 7-dibromo-3-amino-2-naphthoic acid (VIII) and 3 : 7-dibromo-4-nitro-2-naphthoic acid (IX).

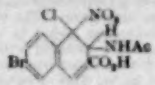


Prager (*Ber.*, 1885, **18**, 2164) found that 4-bromo-2-nitro-1-naphthylamine was converted by hydrobromic acid under pressure into 1 : 2 : 4-tribromonaphthalene. Presumably the milder conditions employed here prevented complete replacement of all the groups by bromine.

4 : 7-Dibromo-3-amino-2-naphthoic acid (VIII) was converted into 3 : 4 : 7-tribromo-2-naphthoic acid (X) by the Sandmeyer reaction. Attempts to decarboxylate this compound, for orientation purposes, by heating the acid with quinoline and copper powder or by direct distillation, failed, the acid being recovered unchanged. The acid (X) was therefore converted into the amide which would not undergo the Hofmann reaction in aqueous media; but in methanol (cf. Windaus, *Ber.*, 1924, **57**, 1731) 3 : 4 : 7-tribromo-2-naphthylamine was formed, and this was deaminated to give 1 : 2 : 6-tribromonaphthalene.

7-Bromo-4-nitro-3-acetamido-2-naphthoic acid (VII) reacted with 20% hydrobromic acid to give an addition compound which has been formulated as 4 : 7-dibromo-4-nitro-3-acetamido-

3 : 4-dihydro-2-naphthoic acid (XI). This compound reacted with 48% hydrobromic acid to give 3 : 7-dibromo-4-nitro-2-naphthoic acid (IX) and with 2*N*-sodium carbonate solution to give 4-nitro-3-hydroxy-2-naphthoic acid. (VII) reacted with constant-boiling hydrochloric acid to give 4-chloro-7-bromo-4-nitro-3-acetamido-3 : 4-dihydro-2-naphthoic acid (XII) which likewise gave 4-nitro-3-hydroxy-2-naphthoic acid on treatment with sodium carbonate solution.

(XI.)  (XII.)

Although there are no references to the addition of halogens or halogeno-acids to nitronaphthols or nitronaphthylamines, Fries and Schimmelschmidt (*loc. cit.*) found that bromonaphthols gave addition compounds with hydrogen bromide.

With regard to the formation of 4-nitro-3-hydroxy-2-naphthoic acid from (XI) and (XII) by the action of alkali, Armstrong and Rossiter (*Proc. Chem. Soc.*, **1891**, **87**—**89**) found that the addition of nitric acid to 1-bromo-2-naphthol gave 1-bromo-1-nitro-2 : 2-dihydroxy-1 : 2-dihydronaphthalene which immediately decomposed to give 1-bromo-1-nitro-2-keto-1 : 2-dihydronaphthalene. This reacted with alkali to give 1-nitro-2-naphthol. 1 : 6-Dibromo-2-naphthol underwent a similar series of reactions but the final product was 6-bromo-1-nitro-2-naphthol. The loss of the 6-bromine atom in our case is therefore unusual. 4-Nitro-3-amino-2-naphthoic acid is probably a precursor of the 4-nitro-3-hydroxy-2-naphthoic acid since Cross and Drew (*loc. cit.*) found that 4-nitro-3-acetamido-2-naphthoic acid was hydrolysed by sodium hydroxide solution to 4-nitro-3-hydroxy-2-naphthoic acid. This reaction has been repeated by using sodium carbonate instead of sodium hydroxide, and a similar result was obtained.

4-Nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid on treatment with bromine (1 mol.) in glacial acetic acid gave 3 : 4 : 7-tribromo-2-naphthoic acid (X), but in an experiment in which 97·5% acetic acid was accidentally used the product consisted of a mixture of unchanged material and 3 : 7-dibromo-4-nitro-2-naphthoic acid (IX). It was found that 1-nitro-2-acetamidonaphthalene on bromination (1 mol.) in glacial acetic acid gave 1 : 2 : 6-tribromonaphthalene (unpublished work). On these grounds 4-nitro-3-acetamido-2-naphthoic acid might have been expected to give 3 : 4 : 7-tribromo-2-naphthoic acid.

Attempts to brominate 4-nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid in chloroform solution failed. In pyridine, however, 3-bromo-1-nitro-2-toluene-*p*-sulphon-naphthalide was formed. Consden and Kenyon (*J.*, **1935**, **1591**) prepared this substance by brominating 1-nitro-2-toluene-*p*-sulphon-naphthalide in pyridine. The introduction of a bromine atom in the 3-position of a naphthalene nucleus is not unusual, cf. Consden and Kenyon (*loc. cit.*) and Bell (*J.*, **1932**, **2734**) who likewise prepared 1 : 3-dibromo-2-toluene-*p*-sulphon-naphthalide.

4 : 7-Dibromo-2-naphthoic acid was prepared from 4 : 7-dibromo-3-amino-2-naphthoic acid (VIII) by deamination. Since it has been shown (unpublished work) that 10% sodium hydroxide at 150° will hydrolyse bromine atoms in a naphthalene ring [cf. Oehler (D.R.-P. 77,446)] 4 : 7-dibromo-2-naphthoic acid was expected to yield 4 : 7-dihydroxy-2-naphthoic acid which on treatment with ammonia and sodium bisulphite would probably yield " carboxy J-acid " (IV) (cf. Bucherer, *J. pr. Chem.*, **1904**, **69**, **83**). The yield of 4 : 7-dibromo-2-naphthoic acid by this method was too low to permit further work so the halogenation of the acetyl and toluene-*p*-sulphonyl derivatives of 3-amino-2-naphthoic acid itself was investigated.

4-Chloro-3-amino-2-naphthoic acid is the only halogenated 3-amino-2-naphthoic acid described in the literature; it has been prepared from 1-chloro-2 : 3-naphthisatin (F.P. 575, 314; *Chem. Zentr.*, **1925**, I, 1021). 2-Acet- and 2-toluene-*p*-sulphon-naphthalide both give 1 : 6-dibromo-derivatives on bromination in acetic acid or chloroform (Bell, *loc. cit.*; Franzen and Stauble, *J. pr. Chem.*, **1921**, **107**, **58**). 3-Toluene-*p*-sulphonamido-2-naphthoic acid was brominated in pyridine to give 4-bromo-3-toluene-*p*-sulphonamido-2-naphthoic acid, which was hydrolysed and decarboxylated to give 1-bromo-2-naphthylamine. Attempts to brominate 4-bromo-3-toluene-*p*-sulphonamido-2-naphthoic acid in glacial acetic acid gave a tribromo-compound, presumably 4 : 5 : 7-tribromo-3-amino-2-naphthoic acid, which was also formed from 3-toluene-*p*-sulphonamido-2-naphthoic acid and bromine (1 mol.) in acetic acid. 3-Acetamido-2-naphthoic acid failed to brominate in glacial acetic acid and was only partly brominated in pyridine, giving an inseparable mixture.

Attempts to nitrate 4-bromo-3-toluene-*p*-sulphonamido-2-naphthoic acid, to give the 7-nitro-compound failed, even in the presence of a boron trifluoride catalyst.

Experimental.

(Analyses are by Mr. E. S. Morton. M. p.s are uncorrected.)

Nitro-derivatives of 3-*Amino-2-naphthoic acid.*

3-*Toluene-p-sulphonamido-2-naphthoic Acid.*—A solution of 3-amino-2-naphthoic acid (250 g.) in water (2·5 l.) and 10*N*-sodium hydroxide (135 c.c.) was filtered, the filtrate heated to 75° and toluene-*p*-sulphonyl chloride (275 g.) gradually added while the mixture was kept slightly alkaline to litmus by the addition of sodium carbonate. The boiling mixture was made alkaline to brilliant-yellow paper and filtered. The hot filtrate was added to water (300 c.c.) and concentrated hydrochloric acid (300 c.c.), and the solid was collected, washed with water, and dried. Crystallisation of this first from glacial acetic acid (1360 c.c.) then from methanol gave 3-*toluene-p-sulphonamido-2-naphthoic acid* as creamy white prisms (238 g.), m. p. 224° (Found: C, 63·5; H, 4·35; N, 4·0. $C_{18}H_{15}O_4NS$ requires C, 63·4; H, 4·4; N, 4·1%).

4-*Nitro*-3-*toluene-p-sulphonamido-2-naphthoic Acid.*—The sulphonamido-compound (51 g.) in glacial acetic acid (150 c.c.) was heated to 100°, then cooled to 54° with stirring. Sodium nitrite (0·1 g.) was added, followed by nitric acid (12·6 c.c.; *d* 1·4), the temperature being held at 54—57°. The solution was cooled to 10°, and the product was collected, washed with glacial acetic acid and carbon tetrachloride, and dried. Crystallisation of the solid from glacial acetic acid gave pale yellow prisms (39 g.), m. p. 188° (decomp.), of 4-*nitro*-3-*toluene-p-sulphonamido-2-naphthoic acid* (Found: C, 56·1; H, 3·8; N, 7·4. $C_{18}H_{14}O_6N_2S$ requires C, 56·0; H, 3·65; N, 7·25%).

4-*Nitro*-3-*amino-2-naphthoic Acid.*—The foregoing toluene-*p*-sulphonyl compound (30 g.) was dissolved in concentrated sulphuric acid (60 c.c.) at 30—40°, the solution poured on to ice, and the solid collected, washed with water, and dried. Crystallisation of the product from methanol gave orange needles (15 g.), m. p. 243—244° [Cross and Drew, *loc. cit.*, gave m. p. 240° (decomp.)] (Found: C, 57·3; H, 3·8; N, 12·1. Calc. for $C_{11}H_8O_4N_2$: C, 56·9; H, 3·45; N, 12·1%).

4 : 7-*Dinitro*-3-*toluene-p-sulphonamido-2-naphthoic Acid.*—4-Nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid (19·3 g.) was boiled with glacial acetic acid (50 c.c.), cooled to 60°, and nitric acid (3·5 c.c.; *d* 1·5) added. The mixture was heated to 100° whereupon a reaction began. After 5 minutes the solution was cooled to 10°, and the solid collected, washed with glacial acetic acid then with carbon tetrachloride, and dried. Crystallisation of the solid from ethyl acetate gave pale yellow needles (3·7 g.), m. p. 177° (explosion), of 4 : 7-*dinitro*-3-*toluene-p-sulphonamido-2-naphthoic acid* (Found: C, 49·25; H, 2·15. $C_{18}H_{13}O_8N_3S$ requires C, 50·1; H, 3·0%).

4 : 7-*Dinitro*-3-*amino-2-naphthoic Acid.*—The toluene-*p*-sulphonyl derivative (3·6 g.) was dissolved in concentrated sulphuric acid (8 c.c.) at 35—40°, the solution poured on to ice, and the solid collected, washed with water, and dried. Crystallisation of the product from ethyl acetate gave orange microcrystals (2·1 g.), m. p. 302°, of the *dinitroaminonaphthoic acid* (Found: C, 47·4; H, 2·6; N, 14·7. $C_{11}H_5O_6N_3$ requires C, 47·6; H, 2·55; N, 15·2%).

4 : 7-*Dinitro*-2-*naphthoic Acid.*—The 3-amino-compound (1 g.) was deaminated by the method of Hodgson and Walker (*J.*, 1933, 1620). Crystallisation of the *dinitronaphthoic acid* from glacial acetic acid gave yellowish brown micro-crystals (0·4 g.), m. p. 230—231° (Found: C, 50·7; H, 3·1; N, 10·3. $C_{11}H_4O_6N_2$ requires C, 50·4; H, 2·3; N, 10·7%).

Decarboxylation of 4 : 7-*Dinitro*-2-*naphthoic Acid.*—The dinitro-compound (0·2 g.) on being heated with copper bronze (0·2 g.) and quinoline (5 c.c.) for 10 minutes gave 1 : 6-dinitronaphthalene as pale yellow needles (from methanol), m. p. 163—164°, not depressed by admixture with an authentic sample.

3-*Acetamido*-2-*naphthoic Acid.*—3-Amino-2-naphthoic acid (100 g.), dissolved in water (800 c.c.) and 10*N*-sodium hydroxide (50 c.c.), was treated at 40° with acetic anhydride (80 c.c.). After the solution had been stirred for 1 hour excess of hydrochloric acid was added, and the solid was collected, washed with water, and dried. It was purified by treatment with boiling methanol, and dried. The product (90 g.) had m. p. 234—235°. An analytical specimen crystallised from ethanol in pale yellow needles, m. p. 237—238° (lit. gives m. p. 238°) (Found: C, 67·8; H, 4·95; N, 6·55. Calc. for $C_{13}H_{11}O_3N$: C, 68·1; H, 4·8; N, 6·1%).

3-Amino-2-naphthoic acid (2 g.) was heated under reflux with acetic anhydride (4 c.c.) for 2 hours, the solution poured into water, and the product crystallised from ethanol to give 3-acetamido-2-naphthoic acid (1·7 g.), m. p. 237—238°.

4-*Nitro*-3-*acetamido*-2-*naphthoic Acid.*—The following method was found to be preferable to that reported by Cross and Drew (*loc. cit.*). 3-Acetamido-2-naphthoic acid (20 g.) and glacial acetic acid (140 c.c.) were heated to 80° and treated with sodium nitrite (0·1 g.) and nitric acid (8 c.c.; *d* 1·42). The temperature was cautiously raised to 95°, and as soon as a clear solution was obtained the reaction mixture was cooled. After 12 hours the solid (18 g.) was collected, washed with carbon tetrachloride, and dried. Crystallisation of the solid from glacial acetic acid gave rosettes of pale yellow needles, m. p. 199—200° (Found: C, 57·1; H, 3·45; N, 10·0. Calc. for $C_{13}H_{10}O_5N_2$: C, 56·9; H, 3·65; N, 10·2%).

Hydrolysis of the *acetyl* compound (4·4 g.) with a boiling mixture of ethanol (44 c.c.) and concentrated hydrochloric acid (22 c.c.) for 1½ hours gave 4-nitro-3-amino-2-naphthoic acid (2·2 g.), m. p. 243—244°.

Acetylation of 4-*Nitro*-3-*amino*-2-*naphthoic Acid.*—4-Nitro-3-amino-2-naphthoic acid (3 g.) and acetic anhydride (15 c.c.) were heated under reflux for 6 hours and cooled, and the crystalline solid collected. Crystallisation of this from glacial acetic acid gave yellow needles (2·7 g.) of *anhydro*-4-*nitro*-3-*acetamido*-2-*naphthoic acid*, m. p. 234—235°, insoluble in cold, dilute sodium carbonate solution (Found: C, 60·4; H, 3·1; N, 10·9. $C_{13}H_8O_5N_2$ requires C, 60·95; H, 3·1; N, 10·9%).

This compound (0·5 g.) was heated under reflux with water (40 c.c.) for 30 hours, sodium carbonate solution added, the mixture filtered, and the filtrate acidified. The product was collected and crystallised from glacial acetic acid to give pale yellow needles (0·4 g.) of 4-*nitro*-3-*acetamido*-2-*naphthoic acid*, m. p. 199—200°.

Acetylation of 4 : 7-*Dinitro*-3-*amino*-2-*naphthoic Acid.*—4 : 7-Dinitro-3-amino-2-naphthoic acid (1 g.) and acetic anhydride (5 c.c.) were heated under reflux for 1 hour, water was added, and the solid was

collected and crystallised from glacial acetic acid to give creamy white needles (0·8 g.) of *anhydro*-**4 : 7-*dinitro*-3-*acetamido*-2-*naphthoic acid***, m. p. 202—203°, insoluble in cold, dilute sodium carbonate solution (Found : C, 51·4; H, 2·65; N, 13·7. $C_{13}H_7O_8N_3$ requires C, 51·8; H, 2·3; N, 14·0%).

This compound (0·1 g.) and water (40 c.c.) were heated under reflux for 18 hours, sodium carbonate was added, the mixture was filtered, and the filtrate was acidified. Crystallisation from glacial acetic acid of the solid so obtained gave yellow micro-crystals of **4 : 7-*dinitro*-3-*acetamido*-2-*naphthoic acid***, m. p. 262° (Found : C, 48·6; H, 3·25; N, 12·6. $C_{13}H_9O_7N_3$ requires C, 48·9; H, 2·8; N, 13·1%).

4 : 7-Dinitro-3-amino-2-naphthoic acid (0·5 g.), treated with acetic anhydride (5 c.c.) and concentrated sulphuric acid (0·2 c.c.), gave the acetyl derivative, m. p. 261—262°.

Halogenated Nitro-derivatives of **3**-*Amino*-**2**-*naphthoic Acid*

***7*-*Bromo*-4-*nitro*-3-*acetamido*-2-*naphthoic Acid*.**—(*a*) Bromine (18·6 c.c.) in glacial acetic acid (50 c.c.) was added to a boiling solution of 4-nitro-3-acetamido-2-naphthoic acid (100 g.) in glacial acetic acid (1220 c.c.). A vigorous reaction took place, and after 15 minutes the solution was cooled in ice and the solid collected. Crystallisation of this from glacial acetic acid gave pale yellow needles (82 g.; 63·5%), m. p. 228—229° (Found : C, 43·7; H, 2·75; N, 7·45; Br, 23·5. $C_{13}H_9O_6N_3Br$ requires C, 44·1; H, 2·55; N, 7·9; Br, 22·5%).

(*b*) The same quantities were used but the mixture was heated under reflux for 1 hour after the addition of the bromine. The yield was 53·7%.

(*c*) The time of heating under reflux was increased to 2½ hours, and the yield obtained was 45·5%.

The acetic acid mother liquors were diluted with water, and the resulting sticky solid was crystallised from methanol giving 4-nitro-3-amino-2-naphthoic acid (26·5%). The methanol mother liquors were concentrated, and the residue heated under reflux with ethanol (200 c.c.) and concentrated hydrochloric acid (100 c.c.) for 2 hours. Water was added, and the solid was collected and crystallised from glacial acetic acid to give 4-nitro-3-amino-2-naphthoic acid (16%).

Bromination of* 4-*Nitro*-3-*toluene*-p-*sulphonamido*-2-*naphthoic Acid in Glacial Acetic Acid*.**—4-Nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid (38·6 g.) was dissolved in boiling glacial acetic acid (250 c.c.) and bromine (5·4 c.c.; 1 mol.) added. After the solution had been heated under reflux for 6 hours it was cooled and the solid (12 g.) collected. Crystallisation of this from glacial acetic acid gave pale cream needles of **3 : 4 : 7-*tribromo*-2-*naphthoic acid, m. p. 244—245° (Found : C, 33·0; H, 1·4; Br, 58·7. $C_{11}H_4O_4Br_3$ requires C, 32·3; H, 1·2; Br, 58·6%).

Orientation of* 3 : 4 : 7-*Tribromo*-2-*naphthoic Acid*.**—(a) **3 : 4 : 7-*Tribromo*-2-*naphthoamide. The acid (14 g.) in benzene (40 c.c.) was heated under reflux with thionyl chloride (4 c.c.) for 7 hours, the solution cooled, and excess of ammonium carbonate added. After 2 hours the benzene was removed by steam, and the solid was collected and washed with hot water. Crystallisation of this from β-ethoxyethanol gave white micro-crystals of the ***amide*** (10 g.), m. p. >280° (Found : C, 32·2; H, 1·75; N, 3·7. $C_{11}H_4ONBr_3$ requires C, 32·3; H, 1·5; N, 3·4%).

(b) **3 : 4 : 7-*Tribromo*-2-*naphthylamine***. The amide (9·3 g.) was suspended in methanol (100 c.c.) and sodium hypochlorite solution (17 c.c.; 15%) added, the temperature rising to 45°. After 15 minutes, 10N-sodium hydroxide (25 c.c.) and methanol (40 c.c.) were added. The methanol was removed by distillation and the residue extracted with water. Crystallisation of the ***amine*** from ethanol gave white needles (4·2 g.), m. p. 157—159° (Found : C, 31·4; H, 1·65; N, 3·65. $C_{10}H_6NBr_3$ requires C, 31·6; H, 1·6; N, 3·7%).

The ***acetyl*** derivative, prepared from the amine and acetic anhydride, crystallised from acetic acid in white needles, m. p. 205—206° (Found : C, 34·2; H, 1·85. $C_{12}H_8ONBr_3$ requires C, 34·1; H, 1·9%).

(c) **3 : 4 : 7-*Tribromonaphthalene***. The amine (1·2 g.) was deaminated by the method used for **4 : 7**-dinitro-3-amino-2-naphthoic acid. Crystallisation from acetic acid gave white needles of **3 : 4 : 7**-tribromonaphthalene, m. p. 113—114° not depressed by admixture with an authentic sample.

Bromination of* 4-*Nitro*-3-*toluene*-p-*sulphonamido*-2-*naphthoic Acid in* 97·5% *Acetic Acid*.**—The compound (19·3 g.) was dissolved in boiling acetic acid (125 c.c.), and bromine (2·7 c.c.) added. After the solution had been heated under reflux for 6 hours, and cooled, water (450 c.c.) was added. The solid obtained (11 g.) was dissolved in ethanol and chromatographed on alumina. The upper band was separated, extracted with sodium carbonate, the extract filtered, and the filtrate acidified. The solid (4 g.), m. p. 186—188°, obtained was shown to be unchanged. The lower band was similarly separated. Crystallisation from acetic acid of the solid obtained gave **3 : 7-*dibromo*-4-*nitro*-2-*naphthoic acid (3·2 g.), m. p. and mixed m. p. (see below) 234—236°.

***Bromination of* 1-*Nitro*-3-*toluene*-p-*sulphonamido*-2-*naphthoic Acid in Pyridine*.**—A solution of the compound (7·7 g.) in pyridine (30 c.c.) was cooled to 5° and treated with a cold solution of bromine (1·2 c.c.) in pyridine (10 c.c.). After 15 minutes the solution was run into a mixture of ice and concentrated hydrochloric acid, and the solid was collected and washed with water. Crystallisation of it from dioxan gave orange micro-crystals (3·5 g.) of **3**-bromo-1-nitro-2-toluene-*p*-sulphon-naphthalide, m. p. 229—231° (Consden and Kenyon, *loc. cit.*, give m. p. 237°) (Found : C, 48·5; H, 2·85; N, 6·4; Br, 18·4. Calc. for $C_{17}H_{13}O_4N_2BrS$: C, 48·5; H, 3·1; N, 6·65; Br, 19·0%).

The amine, prepared from the toluene-*p*-sulphonyl derivative by hydrolysis with concentrated sulphuric acid, crystallised from ethanol in red needles, m. p. 100—101° (Consden and Kenyon, *loc. cit.*, give m. p. 105°) (Found : C, 45·0; H, 2·7; N, 10·4. Calc. for $C_{10}H_7O_2N_2Br$: C, 45·0; H, 2·6; N, 10·5%).

Reactions of* 7-*Bromo*-4-*nitro*-3-*acetamido*-2-*naphthoic Acid*.**—(a) ***With sodium carbonate solution. The compound (2 g.) was heated under reflux with 2N-sodium carbonate solution (30 c.c.) for 20 hours, cooled, and acidified with hydrochloric acid. The solid was collected and crystallised from glacial acetic acid to give yellow micro-crystals (1 g.), m. p. >300° (Found : C, 50·95, 51·2; H, 2·95, 3·0; N, 7·95, 7·65; Br, 21·3%). No structural formula can be ascribed to these figures which agree best with $C_{11}H_{11}O_4N_2Br$ (C, 49·6; H, 3·0; N, 7·7; Br, 22·0%) or $C_{14}H_{11}O_5N_2Br$ (C, 51·0; H, 2·95; N, 7·5; Br, 21·4%).

(b) ***With diethylamine***. The compound (3 g.) and diethylamine (35 c.c.) were heated under reflux for 24 hours, the excess of diethylamine removed by distillation, and excess of 2N-sodium hydroxide added. After being heated on a steam-bath for 1 hour the solution was filtered and acidified (litmus)

with acetic acid; the solid was collected and crystallised from glacial acetic acid to give 7-*bromo*-3-*amino*-4-*diethylamino*-2-*naphthoic acid* as a pale brown powder (2 g.), m. p. >310° (Found: C, 53·8, 53·6; H, 4·65, 4·7; N, 8·3, 8·0; Br, 23·1. $C_{15}H_{17}O_2N_3Br$ requires C, 53·4; H, 5·0; N, 8·3; Br, 23·7%).

(c) *With 48% hydrobromic acid.* The compound (10 g.) and hydrobromic acid (90 c.c.; 48%) were heated under reflux for 24 hours and poured into water (500 c.c.). The solid which was collected was fractionally crystallised from glacial acetic acid; it gave a sparingly soluble product, 4 : 7-*dibromo*-3-*amino*-2-*naphthoic acid* (bright yellow needles) (2·0 g.), m. p. 256—257° (Found: C, 37·8; H, 1·95; N, 3·8; Br, 46·7. $C_{11}H_7O_2NBr_2$ requires C, 38·3; H, 2·0; N, 4·1; Br, 46·4%), and an easily soluble portion which crystallised from ethanol to give orange needles (1·5 g.) of 3 : 7-*dibromo*-4-*nitro*-2-*naphthoic acid*, m. p. 236—238° (Found: C, 35·4; H, 1·6; N, 3·45; Br, 43·0. $C_{11}H_5O_4NBr_2$ requires C, 35·2; H, 1·3; N, 3·7; Br, 42·7%).

4 : 7-Dibromo-3-amino-2-naphthoic acid (1·0 g.) in glacial acetic acid (8·0 c.c.) was added to a solution of sodium nitrite (0·35 g.) in concentrated sulphuric acid (3·5 c.c.) at 20—25°. The diazo-compound was then added to cuprous bromide (1 g.) in hydrobromic acid (10 c.c.; 48%), the mixture was stirred for 1 hour, water added, and the solid collected. Crystallisation of this from acetic acid gave 3 : 4 : 7-tribromo-2-naphthoic acid, m. p. and mixed m. p. 244—245°.

By a similar reaction 4 : 7-dibromo-3-amino-2-naphthoic acid (0·6 g.) gave 3-*chloro*-4 : 7-*dibromo*-2-*naphthoic acid* as pale yellow needles (0·3 g.), m. p. 234—236°, from acetic acid (Found: C, 36·0; H, 1·5. $C_{11}H_5O_2ClBr_2$ requires C, 36·2; H, 1·4%).

4 : 7-Dibromo-3-amino-2-naphthoic acid (1 g.) was deaminated by Hodgson and Walker's method (*loc. cit.*) giving 4 : 7-*dibromo*-2-*naphthoic acid* (0·6 g.), m. p. 258—259° (Found: C, 39·9; H, 2·15. $C_{11}H_6O_2Br_2$ requires C, 40·0; H, 1·8%).

(d) *With dilute hydrobromic acid.* The compound (7 g.) was heated under reflux with hydrobromic acid (19 c.c.; 48%) and water (38 c.c.) for 24 hours, water (150 c.c.) was added, and the solid (6·5 g.) was collected. Crystallisation of this from glacial acetic acid gave pale yellow micro-needles (3·8 g.) of 4 : 7-*dibromo*-4-*nitro*-3-*acetamido*-3 : 4-*dihydro*-2-*naphthoic acid*, m. p. 240—242° (Found: C, 35·6; H, 2·5; N, 6·2; Br, 36·3. $C_{13}H_{10}O_4N_2Br_2$ requires C, 35·9; H, 2·3; N, 6·45; Br, 36·8%).

This compound (1·3 g.) was heated under reflux with hydrobromic acid (25 c.c.; 48%) for 20 hours and diluted with water. The solid (1 g.) was crystallised from acetic acid and gave orange needles, m. p. 234—236°, of 3 : 7-dibromo-4-nitro-2-naphthoic acid.

The compound (0·5 g.) was heated under reflux with 2*N*-sodium carbonate (20 c.c.) for 6 hours, hydrochloric acid was added, and the solid was collected; it crystallised from acetic acid in yellow needles (0·2 g.) of 4-*nitro*-3-*hydroxy*-2-*naphthoic acid*, m. p. 234—236° not depressed by admixture with an authentic sample (Found: C, 56·4; H, 3·2; N, 5·9. Calc. for $C_{11}H_7O_5N$: C, 56·5; H, 3·0; N, 6·0%).

(e) *With hydrochloric acid.* The compound (7 g.), concentrated hydrochloric acid (140 c.c.), and water (70 c.c.) were heated under reflux for 24 hours, water (150 c.c.) was added, and the solid was collected, boiled with ethanol (100 c.c.), and filtered off. 4-*Chloro*-7-*bromo*-4-*nitro*-3-*acetamido*-3 : 4-*dihydro*-2-*naphthoic acid* (3·5 g.) crystallised from acetic acid as creamy white needles, m. p. 239—240° (Found: C, 39·7, 40·0; H, 2·25, 2·4; N, 6·95, 7·3; Cl + Br, 28·6. $C_{13}H_{10}O_5N_2ClBr$ requires C, 40·05; H, 2·6; N, 7·2; Cl + Br, 29·7%).

This compound on hydrolysis with 2*N*-sodium carbonate gave 4-nitro-3-hydroxy-2-naphthoic acid.

(f) *With hydrochloric acid and ethanol.* The compound (10 g.), ethanol (200 c.c.), and concentrated hydrochloric acid (75 c.c.) were heated under reflux for 48 hours and water was added. The resultant solid was dissolved in methanol and chromatographed on alumina. A band, which remained at the top of the column, was extracted with sodium carbonate, acidified, and crystallised from ethanol giving 4-nitro-3-amino-2-naphthoic acid (2·0 g.), m. p. and mixed m. p. 238—240°. The remaining material was isolated by concentration of the eluate, and the solid crystallised from methanol to give orange needles (1 g.), m. p. 103—104°, of 4-*nitro*-3-*amino*-7-*ethoxy*-2-*naphthoic acid* (Found: C, 56·9; H, 4·1; N, 10·65. $C_{13}H_{13}O_5N_2$ requires C, 56·5; H, 4·35; N, 10·2%).

Bromo-derivatives of 3-Amino-2-naphthoic Acid.

4-*Bromo*-3-*toluene*-*p*-*sulphonamido*-2-*naphthoic Acid.*—3-Toluene-*p*-sulphonamido-2-naphthoic acid (8·5 g.) was dissolved in pyridine (40 c.c.), and an ice-cold solution of bromine (1·3 c.c.) in pyridine (10 c.c.) added. Next morning the solution was poured into excess of hydrochloric acid, and the solid was collected and crystallised from glacial acetic acid to give the 4-*bromo*-compound as pale yellow needles, m. p. 197—198° (5 g.) (Found: C, 51·7; H, 3·55; N, 3·75. $C_{18}H_{14}O_4NBrS$ requires C, 51·4; H, 3·3; N, 3·4%).

4-*Bromo*-3-*amino*-2-*naphthoic Acid.*—The toluene-*p*-sulphonyl compound (5 g.) was dissolved in concentrated sulphuric acid (10 c.c.) at 35—40°, the solution poured on to ice, and the solid collected. Crystallisation of this from glacial acetic acid gave bright yellow needles (2 g.), m. p. 220—222° (Found: C, 49·1; H, 3·05; N, 5·7. $C_{11}H_8O_2NBr$ requires C, 49·6; H, 3·0; N, 5·25%).

On decarboxylation in quinoline in the presence of copper bronze, 1-bromo-2-naphthylamine, m. p. and mixed m. p. with an authetic sample 61—63°, was obtained.

4 : 5 : 7(?)-*Tribromo*-3-*amino*-2-*naphthoic Acid.*—(*a*) 3-Toluene-*p*-sulphonamido-2-naphthoic acid (10·2 g.) in boiling glacial acetic acid (100 c.c.) was treated with bromine (4·6 c.c.; 3 mols.). After being heated under reflux for 1 hour the solution was cooled and the solid (8 g.) collected. Crystallised from glacial acetic acid it gave yellow micro-crystals, m. p. 254°, of a *tribromo*-compound (Found: C, 30·9; H, 1·9; N, 3·3; Br, 56·0. $C_{11}H_4O_2NBr_3$ requires C, 31·2; H, 1·4; N, 3·3; Br, 56·6%).

(*b*) 4-Bromo-3-toluene-*p*-sulphonamido-2-naphthoic acid (4·1 g.) in boiling glacial acetic acid (20 c.c.) was treated with bromine (0·5 c.c., 1 mol.). After being heated under reflux for 30 minutes the solution was cooled and the solid collected. Crystallisation of this from acetic acid gave 2 g. of a solid, m. p. 253—254°, identical with the previous compound.

RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
BLACKLEY, MANCHESTER, 9.

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199. *Amine-N-glycosides. Part I. Arylamine-N-glucosides.*

By JOHN HONEYMAN and A. R. TATCHELL.

Aniline and glucose react under various conditions to give the same aniline-*N*-glucoside, which mutarotates in several solvents. Acetylation of aniline-*N*-glucoside gives a mixture of α- and β-aniline-*N*-glucopyranoside tetra-acetates which can be deacetylated to the original aniline-*N*-glucoside.

p-Toluidine-*N*-glucoside is obtained in a pure crystalline form which has been acetylated to β-*p*-toluidine-*N*-glucopyranoside tetra-acetate.

The pyranose ring structure of these amine-*N*-glucosides is probable, but not certain.

THE reaction products obtained when sugars react with amines have been known for many years, but although much work has been carried out to determine their structure there is still no clear picture of their nature. The early workers (Schiff, *Annalen*, 1870, **154**, 30; Sorokin, *Ber.*, 1886, **19**, 513) prepared compounds whose structures were considered to be of the Schiff's base type (Schiff and Straus, *Ber.*, 1894, **27**, 1287) or of the cyclic glycosidic type (Marchlewski, *J. prakt. Chem.*, 1894, [ii], **50**, 95). The methylation studies of Irvine and his co-workers from 1908 to 1911 (*e.g.*, Irvine and Hynd, *J.*, 1911, **99**, 161) furnished strong evidence of the cyclic nature of these compounds. Their isolation of tetramethyl aniline-*N*-glucopyranoside was held to be evidence for considering the mutarotating aniline-*N*-glucoside to be α- and β-aniline-*N*-glucopyranosides. Since then, certain arylamine-*N*-pentosides have been prepared which have been assigned the furanose structure solely on the basis of their reaction with triphenylmethyl chloride. In particular, certain arylamine-*N*-pentosides have thus been held to be furanosides (Kuhn and Ströbele, *Ber.*, 1937, **70**, 773) although later workers claim to have shown that at least one of these is actually a pyranoside (mentioned by Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, 855, but details not yet published). Similarly, xylidine-*N*-riboside prepared in boiling alcohol is considered to be a furanoside (Kuhn and Birkofer, *Ber.*, 1938, **71**, 621), whereas the xylidine-*N*-riboside prepared in alcohol at room temperature is thought to be a pyranoside (Berger and Lee, *J. Org. Chem.*, 1946, **11**, 75). Under similar conditions aniline reacts with ribose to give two aniline-*N*-ribosides (Berger and Lee, *loc. cit.*); these were cyclic because acetylation of each led to a triacetate; although the triacetates were glasses, no characteristic physical data were given, and they had acetyl contents somewhat lower than the theoretical. Berger and Lee held that they were distinct compounds. Removal of the aniline residue from each gave two amorphous ribose triacetates (Berger, Solmssen, Leonard, Wenis, and Lee, *J. Org. Chem.*, 1946, **11**, 91). These workers considered them to be ribose 2 : 3 : 4-triacetate (from aniline-*N*-ribopyranoside) and ribose 2 : 3 : 5-triacetate (from aniline-*N*-ribofuranoside). Examination of the data of these workers shows that one of the compounds, with acetyl content 40·9% (theoretical, 40·7%), had $[\alpha]_D^{20}$ −26·3°, while the other, of acetyl content 41·5%, had $[\alpha]_D^{20}$ −24·2°. It is considered, therefore, that there is no evidence that two distinct aniline-*N*-riboside triacetates have been prepared. On the contrary, other workers (Todd *et al.*, *loc. cit.*) have shown that the two aniline-*N*-ribosides are acetylated to the same aniline-*N*-ribopyranoside 2 : 3 : 4-triacetate. Furthermore, Berger and Lee have shown that benzoylation of the two aniline-*N*-ribosides, followed by hydrogenation, gives the same ribitylaniline tribenzoate. The sole remaining chemical evidence for the pyranose and furanose structures assigned to the aniline-*N*-ribosides rests on the reaction of the compounds with triphenylmethyl chloride. This reagent is now known to be unsatisfactory for detecting primary alcohol groups such as would be present in aniline-*N*-ribofuranoside and absent in aniline-*N*-ribopyranoside, for it reacts with secondary as well as with primary alcohol groups (Hockett and Hudson, *J. Amer. Chem. Soc.*, 1931, **53**, 4456; McIlroy, *J.*, 1946, 100). Crystalline triphenylmethyl derivatives of β-methylxylopyranoside, a compound similar in structure to aniline-*N*-ribopyranoside, have been isolated (Jackson, Hockett, and Hudson, *J. Amer. Chem. Soc.*, 1934, **56**, 947).

Indeed, the work of Berger and Lee really confirms the unsatisfactory nature of this reagent. From the compound they consider to be aniline-*N*-ribofuranoside they isolated a tan-coloured amorphous product giving the elementary analysis of a monotrityl aniline-*N*-riboside combined with 1·75 molecules of water. No attempt was made to show that the trityl residue was attached to $C_{(5)}$. Under similar conditions the aniline-*N*-ribopyranoside gave a tarry product which could not be purified. It is clear that Berger and Lee have not shown that this second isomer reacts less readily with triphenylmethyl chloride. Methylation studies have been unproductive (Berger and Lee, *loc. cit.*), probably because of the instability of the *N*-glycosides to alkali. Oxidation with periodate has also been found to be of no value (Berger and Lee, *loc. cit.*; Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, 861). It seems fair to say, therefore, that there

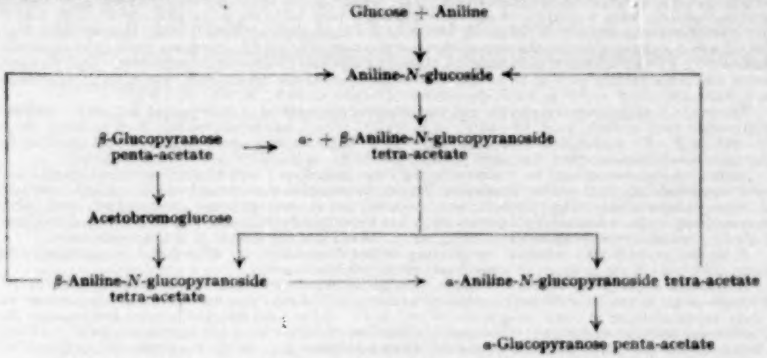
has been no chemical evidence presented so far for assigning the furanose structure to one of the aniline-*N*-ribosides. No derivative with this structure has been isolated. Of the physical data the melting points, as Berger and Lee point out, are unreliable. For **3**: 4-xylidine-*N*-ribofuranoside Kuhn and Birkofer (*loc. cit.*) give m. p. 118°, whereas this compound prepared identically was found by Berger and Lee to have m. p. 128—130°. The corresponding pyranoside of these workers has m. p. 110—112°. For aniline-*N*-ribopyranoside Todd and his co-workers give m. p. 119°, whereas Berger and Lee give m. p. 125—127°. For the corresponding furanoside the former workers give m. p. 126—127°, whereas the latter record m. p. 138—140°. In addition, Berger and Lee have found that mixing the two aniline-*N*-ribosides does not, as a rule, lead to a depressed melting point.

It remains to consider the specific rotations, and here lies the sole evidence for the existence of the two ring-isomers of arylamine-*N*-ribosides. The **3**: 4-xylidine-*N*-ribopyranoside has $[\alpha]_D^{20}$ +171·7° ⟶ +56·5° (*c*, 0·5 in pyridine), while the corresponding furanoside has $[\alpha]_D^{20}$ +94·5° ⟶ +53·0° (*c*, **1** in pyridine). The final values are so close that no conclusion that they represent α- + β-ribopyranosides and α- + β-ribofuranosides, respectively, is tenable. It might as well be that the former compound is, say, pure α-pyranoside mutarotating to an equilibrium mixture of α- + β-pyranoside, whereas the latter is a mixture of α- and β-pyranosides, richer in the β-anomer, mutarotating to the same equilibrium mixture of α- + β-pyranosides. With the aniline-*N*-ribosides the difference in specific rotation is marked and appears to be conclusive. The product of condensation in boiling alcohol, considered by Berger and Lee to be aniline-*N*-ribofuranoside, has $[\alpha]_D^{20}$ +176·5° ⟶ +156·6° (*c*, **3** in pyridine) (Berger and Lee; Todd *et al.*), whereas the product of condensation in alcohol at room temperature, considered to be the pyranoside, has $[\alpha]_D^{20}$ +63·4° ⟶ +48·6° (*c*, **1** in pyridine) (Berger and Lee; Todd *et al.*), and, since the two compounds mutarotate in the same direction but not to the same final equilibrium value, there appears to be a strong case for believing that two different ring-isomers have been obtained. There is, however, no acceptable evidence for deciding which has the furanose and which the pyranose structure. Thus, Berger and Lee's belief that the pyranose compound was converted into the more stable furanose compound simply by refluxing in alcohol or slowly at room temperature in alcohol, or by drying over phosphoric oxide in a vacuum, requires further investigation. (This investigation has already been begun in our laboratories.)

The case of the aniline-*N*-D-arabinosides must also be mentioned. The product of condensation in alcohol at room temperature, considered by Berger and Lee (*J. Org. Chem.*, 1946, **11**, 84), by analogy with the ribosides, to be aniline-*N*-arabinopyranoside, has m. p. 130°, $[\alpha]_D^{20}$ +8·9° ⟶ −13·2° (*c*, 1·9 in methanol, after 48 hours), $[\alpha]_D^{20}$ +68° ⟶ −4·2° (*c*, **3** in pyridine, after 48 hours). The product, prepared in boiling alcohol by following the same procedure as an earlier worker [Hanaoka, *J. Biochem.* (*Japan*), 1940, **31**, 95], had m. p. 130°, $[\alpha]_D^{20}$ +27·4° ⟶ −8·0° (*c*, 1·6 in methanol, after 24 hours), $[\alpha]_D^{20}$ +82° ⟶ +1·48° (*c*, **2** in pyridine, after 24 hours). Hanaoka cites m. p. 130°, $[\alpha]_D^{20}$ +34° ⟶ +2·5° (*c*, 1 in methanol). Again the values are too similar for certainty that different ring forms are present: the alternative explanation advanced in the case of the xylidine-*N*-ribosides appears to be equally valid.

It was in the light of the papers discussed above that the present work was started. During the course of this investigation it has been found that glucose reacts with aniline in boiling alcohol (Sorokin, *loc. cit.*), in aqueous alcohol at room temperature, and in boiling water (Weygand, *Ber.*, 1939, **72**, 1663), to give the same aniline-*N*-glucoside, mutarotating in methanol from an initial value of about +10° to a final value of about −52°. Despite many attempts to prepare this compound and to obtain it in a pure stable form it has invariably been obtained as a white solid which is not truly crystalline. It is precipitated from several solvents in a jelly-like form from which the last traces of solvent are difficult to remove, owing, it is considered, to the physical form of the product. When dry it is a hard white powder which, however, is unstable, becoming brown on storage at room temperature, even in a vacuum desiccator. Aniline-*N*-glucoside, like all compounds of this type, is readily hydrolysed by dilute acids. It is also attacked by aqueous alkali, and it therefore reduces Fehling's solution rapidly. No reproducible melting point was obtained for this product. Acetylation was successfully achieved with acetic anhydride in pyridine; under somewhat different conditions a similar mixture of tetra-acetates was obtained. The components of the mixture were shown to have pyranose structure since the removal of the aniline residue, followed by acetylation with acetic anhydride and zinc chloride, gave the known α-glucopyranose penta-acetate. Furthermore, the same mixture of aniline-*N*-glucoside tetra-acetates was obtained from α- or β-glucopyranose penta-acetate by hydrolysing the acetyl group from $C_{(1)}$ and treating the product with aniline (Frèrejacque, *Compt. rend.*, 1936,

202, 1190). This mixture of aniline-*N*-glucopyranoside tetra-acetates, while differing somewhat in melting range and specific rotation in different preparations, was invariably separable by fractional crystallisation or through the carbon tetrachloride complex of one of them (Frérejacque, *loc. cit.*) into the two pure isomers. One of these, also obtained when acetobromoglucose reacts with aniline, is β-aniline-*N*-glucopyranoside, m. p. 97—98°, $[\alpha]_D^{18}$ −57° (*c*, 0·4 in chloroform); the other is α-aniline-*N*-glucopyranoside tetra-acetate, m. p. 149—150°, $[\alpha]_D^{18}$ +179° (*c*, 0·4 in chloroform). When the β-form is kept in methanol containing a trace of aqueous ammonia at room temperature it is slowly converted into the less soluble α-anomer. All the tetra-acetates mentioned here are deacetylated by methanol containing aqueous ammonia to the same aniline-*N*-glucoside which is obtained by direct condensation. These experiments show that aniline-*N*-glucoside is a mixture which reacts, when acetylated in pyridine, in the pyranose form only. It would appear probable although not certain, therefore, that the aniline-*N*-glucosides mentioned are mixtures of α- and β-aniline-*N*-glucopyranoside. These reactions are summarised in the annexed chart.



When *p*-toluidine is used instead of aniline rather different results are obtained. Thus, although prepared by different workers by different methods, only one *p*-toluidine-*N*-glucoside has been isolated which has well-defined crystalline form and sharp melting point. Acetylation of this glucoside has now been found to give a single tetra-acetate, m. p. 145—146°, $[\alpha]_D^{18}$ −34·2° in chloroform, which must be a derivative of β-*p*-toluidine-*N*-glucopyranoside, since it is identical with the compound prepared from acetobromoglucose and *p*-toluidine.

Although *p*-toluidine-*N*-glucoside is more stable than the corresponding aniline compound they both decompose on storage at room temperature. After about a year in specimen tubes both substances have decomposed to black tars. However, the tetra-acetates of both are stable at room temperature.

In all the cases recorded so far aniline- and *p*-toluidine-*N*-glucosides react to give derivatives with the pyranose ring-structure.

Experimental.

(The light petroleum used throughout had boiling range 60—80°.)

Aniline-N-glucoside.—Glucose (18 g., 1 mol.) was refluxed in absolute alcohol (150 ml.) with freshly re-distilled aniline (9·3 g., 1 mol.) for 2 hours. On cooling, a solid separated and was collected. This was recrystallised from absolute alcohol and washed with dry ether before being dried in an evacuated desiccator at room temperature. The almost white solid (15 g.), $[\alpha]_D^{18}$ +5·1° ⟶ −51·7° (after 24 hours) (*c*, 1·6 in methanol), melted with decomposition at temperatures varying between 110° and 150°, depending on the rate of heating. A further crop of product (6 g.), $[\alpha]_D^{18}$ +11·25° ⟶ −51·9° (after 24 hours) (*c*, 0·4 in methanol), was obtained by partial concentration of the reaction mother-liquor. Further concentration gave more product (3 g.), $[\alpha]_D^{18}$ +5° ⟶ −52·3° (total yield, 95%). Irvine and Gilmour give $[\alpha]_D$ +10° ⟶ −52° for the first fraction and $[\alpha]_D$ −20·1° ⟶ −52° for later fractions.

Glucose (5 g., 1 mol.) in absolute alcohol (15 ml.) and water (5 ml.) was left at room temperature for a week with aniline (8 g., 3 mols.). The solution was then evaporated to dryness over silica gel in an evacuated desiccator. The solid was purified by repeated washing with cold absolute alcohol and then with ether and dried as above. The appearance of the product (4 g., 53%), $[\alpha]_D^{18}$ +6° ⟶ −52·3° (*c*, 0·4 in methanol), was similar to the previous one.

Aniline-*N*-glucoside, prepared by the method of Weygand (*loc. cit.*), was a cream-coloured powder,

$[\alpha]_D^{\beta}$ +10·3 ⟶ −52·8° (*c*, 0·4 in methanol). Weygand gives m. p. 140°, but does not mention the specific rotation. This method was the normal one used hereafter for preparing aniline-*N*-glucoside.

The solid products were examined microscopically under polarized light and were seen to be non-crystalline.

Mutarotation of Aniline-N-glucoside.—The mutarotation of aniline-*N*-glucoside in methanol and ethanol proceeds smoothly. In dry pyridine no change in rotation takes place but rapid mutarotation in pyridine–acetic acid was observed. The following values were obtained: $[\alpha]_D^{\beta}$ −12·5° (*c*, 2·0 in pyridine); $[\alpha]_D^{\beta}$ −11·3° ⟶ −62·5° (after 24 hours) (*c*, 0·4 in pyridine containing a trace of glacial acetic acid); $[\alpha]_D^{\beta}$ ⟶ −60·0° (equilibrium value after 6 minutes) (*c*, 0·8 in pyridine, 66 ml.; acetic acid 34 ml.).

Aniline-*N*-glucoside, $[\alpha]_D^{\beta}$ +10·5° ⟶ −52·5° (*c*, 0·8 in methanol), was recovered by allowing the methanolic solution to evaporate at room temperature.

Acetylation of Aniline-N-glucoside.—Aniline-*N*-glucoside (20 g.) was dissolved in pyridine, and acetic anhydride (80 ml.) was added gradually at 0°. After 24 hours at room temperature the pyridine solution was poured on ice. After several hours the product was filtered off, washed with water, and dried in a vacuum at room temperature. The crude crystals (23 g., 64%), m. p. 80—85°, were recrystallised from absolute alcohol–light petroleum. During this recrystallisation an oil separated first, followed by a larger crop of crystals, m. p. 92—105°, $[\alpha]_D^{\beta}$ +40·2° (*c*, 2·5 in chloroform). These, after several recrystallisations, were a mixture of aniline-*N*-glucoside tetra-acetates, m. p. 88·5—92·5°, $[\alpha]_D^{\beta}$ +45·8° (*c*, 2·5 in chloroform) (Found: C, 56·4; H, 5·9; N, 3·3. $C_{20}H_{25}O_9N$ requires C, 56·7; H, 5·95; N, 3·3%). The oil which separated during the recrystallisation subsequently solidified and was purified by recrystallisation from a small volume of methanol and then from absolute alcohol–light petroleum. This product, which was subsequently proved to be *α-aniline-N-glucopyranoside tetra-acetate*, was a single substance, m. p. 149—150°, $[\alpha]_D^{\beta}$ +180° (*c*, 2·5 in chloroform) (Found: C, 56·9; H, 6·0; N, 3·3%).

The product of another acetylation was separated by the method of Frérejacque (*loc. cit.*). Aniline-*N*-glucoside tetra-acetate, m. p. 88—92·5°, $[\alpha]_D^{\beta}$ +45·7° (10 g.), was separated into *β*- (6 g., 60%), m. p. 97—98°, $[\alpha]_D^{\beta}$ −57° (*c*, 0·4 in chloroform), $[\alpha]_D^{\beta}$ −68·3° (*c*, 0·4 in 90% aqueous alcohol) and *α*-aniline-*N*-glucopyranoside tetra-acetate (4 g., 40%), m. p. 140—150°, $[\alpha]_D^{\beta}$ +179° (*c*, 0·4 in chloroform).

In another experiment aniline-*N*-glucoside (5 g.) was heated on a water-bath in pyridine (20 ml.) and acetic anhydride (20 ml.). After 20 minutes' heating the solution was allowed to cool and left overnight at room temperature. The product was isolated as in the previous preparation, and after recrystallisations from alcohol–light petroleum it was shown similarly to be a mixture of *α*- and *β*-aniline-*N*-glucopyranoside tetra-acetates (5 g., 62%), m. p. 92—110°, $[\alpha]_D^{\beta}$ +55·3° (*c*, 2·4 in chloroform).

A similar product was obtained by treating aniline-*N*-glucoside for 30 minutes in pyridine with acetic anhydride in the presence of a small amount of perchloric acid.

In another experiment the lævorotatory form of aniline-*N*-glucoside was acetylated. Aniline-*N*-glucoside (5 g.) in pyridine (20 ml.) containing acetic acid (0·5 ml.) was kept at room temperature for 3 days before addition of acetic anhydride (20 ml.) at 0°. After a further day at room temperature the product was isolated as before. After recrystallisations from alcohol–light petroleum there remained a mixture of *α*- and *β*-aniline-*N*-glucopyranoside tetra-acetates (5 g., 62%), m. p. 88—95°, $[\alpha]_D^{\beta}$ +67·4° (*c*, 0·8 in chloroform).

Conversion of β- into α-Aniline-N-glucopyranoside Tetra-acetate.—If a saturated solution of any of the above mixed *α*- and *β*-aniline-*N*-glucopyranoside tetra-acetates, or of the pure *β*-anomer, in methanol containing a drop of aqueous ammonia (10%) was kept at room temperature, then a gradual separation of crystalline material took place. This material, on recrystallisation, was found to be *α*-aniline-*N*-glucopyranoside tetra-acetate (80% yield), m. p. 149—150°, $[\alpha]_D^{\beta}$ +180° (*c*, 0·4 in chloroform).

Conversion of Aniline-N-glucopyranoside Tetra-acetates into α-Glucopyranose Penta-acetate.—The hydrolysis of aniline-*N*-glucopyranoside tetra-acetates was successfully achieved by the method of Berger and Lee (*loc. cit.*). The crude glucose tetra-acetate was obtained as a viscous red syrup (3·5 g., 87%) which did not crystallise. This syrup (2 g.) was heated on a boiling-water bath for 30 minutes with acetic anhydride (25 ml.) and powdered anhydrous zinc chloride (0·5 g.). After being poured into water and kept for several hours the product was extracted with chloroform. The extract was washed free from acid and dried before the chloroform was evaporated off, leaving a syrup which crystallised from alcohol. The product was *α*-glucopyranose penta-acetate (1·7 g., 78%), m. p. 110—111°, $[\alpha]_D^{\beta}$ +100·9°. A mixed m. p. with authentic *α*-glucopyranose penta-acetate, m. p. 110—111°, showed no depression.

Preparation of Aniline-N-glucopyranoside Tetra-acetates from β-Glucopyranose Penta-acetate.—The method of Frérejacque (*loc. cit.*) was used. The product was recrystallised from alcohol–light petroleum and was a mixture of *α*- and *β*-aniline-*N*-glucopyranoside tetra-acetates, m. p. 88—92·5°, $[\alpha]_D^{\beta}$ +46·1° (*c*, 0·9 in chloroform). This mixture was separated by the procedure already described into *α*-aniline-*N*-glucopyranoside tetra-acetate and the corresponding *β*-anomer.

Preparation of β-Aniline-N-glucopyranoside Tetra-acetate from Acetobromoglucose.—The method of Baker (*J.*, 1928, 1583) was used. After recrystallisation from ether–light petroleum there was obtained pure *β*-aniline-*N*-glucopyranoside tetra-acetate, m. p. 96—97°, $[\alpha]_D^{\beta}$ −70·3° (*c*, 0·4 in 90% alcohol), $[\alpha]_D^{\beta}$ −55° (*c*, 0·4 in chloroform). Baker (*loc. cit.*) gives m. p. 98°, $[\alpha]_D^{\beta}$ −73·3° (in 90% alcohol).

Deacetylation of Aniline-N-glucopyranoside Tetra-acetates.—The standard procedure was to allow the tetra-acetate (4 g.) to remain in methanol (40 ml.) containing aqueous ammonia (5 ml., *d* 0·880) at room temperature for 3 days. After removal of the solvent at room temperature under reduced pressure the product was purified by recrystallisation from alcohol. In different experiments *α*-aniline-*N*-glucopyranoside tetra-acetate, the *β*-anomer, and mixtures of *α*- and *β*-anomers were used. In each case aniline-*N*-glucoside was obtained: $[\alpha]_D^{\beta}$ *ca.* +10° ⟶ −52° (in methanol), *i.e.*, identical with the substance prepared directly from glucose and aniline.

p-Toluidine-N-glucoside.—Glucose (5·4 g., 1 mol.) was heated with *p*-toluidine (3·2 g., 1 mol.) and water (1 ml.) on a boiling-water bath until homogeneous (15 minutes). Ether (100 ml.) was added and the precipitated solid (6 g., 86%) filtered off. Recrystallisation from ether–alcohol gave needle-shaped crystals of *p*-toluidine-*N*-glucoside, m. p. 117—118°, $[\alpha]_D^{\beta}$ −101·2° ⟶ −45·8° (*c*, 0·5 in methanol).

This same compound has been obtained by different procedures by Irvine and Gilmour (*J.*, 1909, **95**, 1548) and Kuhn and Dansi (*Ber.*, 1936, **69**, 1745).

β-p-Toluidino-N-glucopyranoside Tetra-acetate.—*β-p*-Toluidine-*N*-glucoside tetra-acetate was prepared from acetobromoglucose by the method of Baker (*loc. cit.*). After recrystallisation from absolute alcohol pure *β-p*-toluidine-*N*-glucopyranoside tetra-acetate was obtained, having m. p. 144—145°, $[\alpha]_D^{18}$ −33·4° (*c*, 0·4 in chloroform).

p-Toluidine-*N*-glucoside (5 g.) was dissolved in pyridine (20 ml.) and acetic anhydride (20 ml.) at 0°. After 24 hours at room temperature the solution was poured on ice. After several hours the solid product was collected and recrystallised from alcohol. This was *β-p*-toluidine-*N*-glucopyranoside tetra-acetate (5 g., 70%), m. p. 145—146°, $[\alpha]_D^{18}$ −34·2° (*c*, 0·5 in chloroform), mixed m. p. with the compound prepared above, 144—145°. For this compound Kuhn and Dansi (*loc. cit.*) cite m. p. 144—145°, $[\alpha]_D^{20}$ −57·5° (in methyl acetate).

UNIVERSITY OF LONDON, KING'S COLLEGE. [*Received, December 19th*, 1949.]

200. *Experiments on the Synthesis of the Pyrethrins. Part III. Synthesis of Dihydrocinerin-I and Tetrahydropyrethrin-I; a Study of the Action of N-Bromosuccinimide on 3-Methyl-2-n-alkyl (and alkenyl)-cyclopent-2-en-1-ones.*

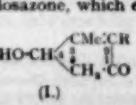
By LESLIE CROMBIE, MICHAEL ELLIOTT, and STANLEY H. HARPER.

3-Methyl-2-*n*-alkylcyclopent-2-en-1-ones with one molecular proportion of *N*-bromosuccinimide undergo monosubstitution at the 4-position, together with some disubstitution (probably at the 4- and the 1'-position), and hence recovery of unchanged ketone. The bromoketone is converted into the acetoxyketone, which is hydrolysed to the (±)-4-hydroxy-3-methyl-2-*n*-alkylcyclopent-2-en-1-one. By this means are prepared (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone (alkyl being butyl and amyl respectively), transformation products of cinerolone and of pyrethrolone, the alcoholic components of the natural pyrethrins. The bromoketones and silver (±)-*trans*-chrysanthemate give racemic dihydrocinerin-I and tetrahydropyrethrin-I which have very little insecticidal action.

The bromo-ketones readily eliminate hydrogen bromide, *e.g.*, with organic bases or sodium methoxide, to give *cyclo*pentadienones, characterised by high-melting derivatives but themselves probably existing only as dimers.

3-Methyl-2-*n*-alkenylcyclopent-2-en-1-ones undergo preferential side-chain substitution with *N*-bromosuccinimide, followed by elimination of hydrogen bromide and polymerisation. 3-Methyl-2-*n*-pent-4'-enylcyclopent-2-en-1-one undergoes very ready disubstitution, followed by elimination of hydrogen bromide. No monomeric product apart from unchanged ketone could be isolated and the method fails as a route to pyrethrolone or cinerolone and analogues containing alkenyl side chains.

THE erroneous formulation of pyrethrolone (Ia) as an α-ketol, with the hydroxyl group in the 5-position, was founded on its reducing properties and the isolation of a supposed *p*-nitrophenylosazone by Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 212). Subsequently, by analogy, cinerolone (Ib) was also formulated as an α-ketol (LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 114). However, LaForge and Soloway (*J. Amer. Chem. Soc.*, 1947, **69**, 186, 2932) showed that synthetic (±)-5-hydroxy-3-methyl-2-*n*-butylcyclopent-2-en-1-one was not identical with naturally derived (±)-dihydrocinerolone and assigned the hydroxyl group to $C_{(4)}$, the only other vacant position in the ring. This structure (Id), with the hydroxyl group in an " allylic " position, accords well with the reactivity of the chloro-ketones obtained by the action of thionyl chloride on cinerolone, dihydrocinerolone, or tetrahydropyrethrolone, and with the ready hydrogenolysis of pyrethrolone acetate, pyrethrolone methyl ether, and the pyrethrins themselves. Further dihydrocinerolone possesses only feeble reducing power and does not yield a *p*-nitrophenylosazone, which excludes the α-ketol formulation.



(I.)

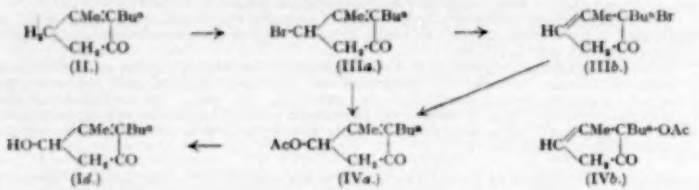
Ia, R = $CH_2{\cdot}^{\gamma}CH{:}^{\beta}CH{\cdot}^{\alpha}CH{:}CH_2$
Ib, R = $CH_2{\cdot}CH{:}CHMe$
Ic, R = $CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Me$
Id, R = $CH_2{\cdot}CH_2{\cdot}CH_2Me$

Some confirmation of the correctness of the proposed structure was obtained by Soloway and LaForge (*ibid.*, p. 979) who synthesised a ketol by refluxing dihydrocinerone with *N*-bromosuccinimide in carbon tetrachloride for 18 hours and hydrolysing the crude bromo-ketone with an aqueous suspension of chalk. The semicarbazone and 3 : 5-dinitrobenzoate of this ketol were identical (mixed melting points) with those from naturally derived (±)-dihydrocinerolone. This work was reported briefly without experimental details and no amplification has yet been

published. Shortly afterwards Dauben and Wenkert (*ibid.*, p. 2075) described briefly the synthesis of the higher homologue, (±)-tetrahydropyrethrolone, by a similar route from tetrahydropyrethrone, but using only a 30-minutes reaction period and hydrolysing the bromo-ketone with an aqueous suspension of barium carbonate. They also prepared the acetoxy-ketone by reaction of the bromo-ketone with silver acetate.

This paper describes a study of the bromo-compounds obtained by the action of *N*-bromosuccinimide on dihydrocinerone, tetrahydropyrethrone, and related ketones, made in connection with the synthesis of racemic dihydrocinerin-I and tetrahydropyrethrin-I, during which we have prepared (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone.

We found that dihydrocinerone reacted to completion in a few minutes with *N*-bromosuccinimide in boiling carbon tetrachloride, neither benzoyl peroxide nor ultra-violet irradiation being necessary. After removal of succinimide and solvent, the undistilled bromo-ketone was refluxed with silver acetate in glacial acetic acid. Fractional distillation of the product gave the *acetoxyketone* [(±)-*dihydrocineronyl acetate*] in 60% overall yield from dihydrocinerone. Since there was also a forerun of dihydrocinerone and the recovery of succinimide had been quantitative, it was suspected that di- or poly-bromination had occurred. This suspicion was confirmed, for the highest-boiling fraction had a carbon and a hydrogen content tending towards that calculated for a diacetoxy-ketone. Further, distillation of the bromination product resolved it into unchanged dihydrocinerone, *monobromodihydrocinerone* (the main product), intermediate fractions, and a final fraction with a bromine content approaching that calculated for a dibromodihydrocinerone. Dibromination, which was not mentioned by Soloway and LaForge or by Dauben and Wenkert, is not surprising since two allylic methylene groups (the 4 and 1′) are available for free-radical substitution. Attempts to hydrolyse the acetoxy-ketone by prolonged refluxing with aqueous suspensions of barium carbonate were not successful (contrast Dauben and Wenkert above), but brief hydrolysis with methanolic potassium hydroxide gave (±)-dihydrocinerolone which was characterised as its semicarbazone and 3 : 5-dinitrobenzoate. The overall yield from ketone to ketol was 44%.



Similarly, tetrahydropyrethrone reacted rapidly and smoothly with one molecular proportion of *N*-bromosuccinimide, and the undistilled bromo-ketone gave, as above, tetrahydropyrethronyl acetate and (±)-tetrahydropyrethrolone, which was similarly characterised. This product did not react with lead tetra-acetate in acetic acid in the presence of water and is not therefore an α-ketol (cf. Baer and West, *J.*, 1949, 93). We also found that tetrahydropyrethrone reacted smoothly and completely with two molecular proportions of *N*-bromosuccinimide, without evolution of hydrogen bromide, and the dibromo-ketone so obtained reacted with yet another molecular proportion of *N*-bromosuccinimide in the presence of a trace of benzoyl peroxide.

Comparison of the physical properties and derivatives of our synthetic hydroxy-ketones with those of the corresponding naturally derived compounds shows satisfactory concordance (see *Nature*, 1948, **162**, 222) and in conjunction with the mixed melting points determined by Soloway and LaForge (*loc. cit.*) leaves no doubt as to the identity of our products with naturally derived (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone.

In the communications of Soloway and LaForge (*loc. cit.*) and of Dauben and Wenkert (*loc. cit.*) no conclusive evidence or reasoned argument was given to support the assumption that bromination occurs in the 4-position of the ring and that the resultant ketols are 4-hydroxy-3-methyl-2-alkylcyclopent-2-en-1-ones. We have shown that substitution can occur in more than one position. Apart from the 4-methylene group, as pointed out above, the 1′-methylene group should be prone to substitution by free-radical reagents, while substitution at the 3-methyl group and at the 5-methylene group is conceivable though less likely. Strong evidence against the hydroxy-group derived from bromination with one molecular proportion of *N*-bromosuccinimide being elsewhere than at $C_{(4)}$ has been adduced (Harper, *Ann. Reports*, 1948, **45**, 162). The

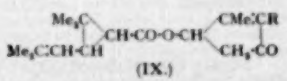
4-hydroxy-structure of (±)-dihydrocinerolone has since been directly proved by synthesis: the cyclisation of (±)-3-hydroxy-n-decane-2 : 5-dione gives a product identical with the naturally derived material and with the ketol prepared by the *N*-bromosuccinimide route (mixed melting points of the 3 : 5-dinitrobenzoates) (Schechter, Green, and LaForge, *J. Amer. Chem. Soc.*, 1949, **71**, 3165; Crombie, Edgar, Harper, and Lowe, forthcoming publication). Although this establishes that bromination occurs initially at the 4-methylene group, it does not follow that the following stages necessarily take the direct course (II ⟶ IIIa ⟶ IVa ⟶ Id): there is a known tendency for the products of *N*-bromosuccinimide substitution to undergo allylic rearrangements (IIIa ⟶ IIIb), and for anionotropic rearrangement to occur (IIIa ⟶ IVb, or IIIb ⟶ IVa) on subsequent conversion into the acetoxy-ketones. That the acetoxy-ketone has the structure (IVa) is shown by its identity with naturally derived (±)-dihydrocineronyl acetate, prepared by catalytic reduction of (±)-cineronyl acetate which has been proved spectroscopically to contain an αβ-unsaturated carbonyl group (West, *J.*, 1946, 463). It is also known that in the alkaline hydrolysis of such esters, through acyl–oxygen fission, no rearrangement occurs. Any scheme involving (IVb) is therefore excluded.

The evidence excluding the participation of (IIIb) is less conclusive. LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 222) converted (±)-dihydrocinerolone by thionyl chloride into a chloro-ketone, and dehalogenation of this with zinc in ethanol gave the unrearranged ketone, dihydrocinerone (II). If this is the reverse of the direct hydrolysis of the bromo-ketone to (±)-dihydrocinerolone (Soloway and LaForge, *loc. cit.*), then participation of (IIIb) is unlikely. No closely analogous system has been investigated in detail. Burton and Shoppee (*J.*, 1934, 201; cf. Allen and Spanagel, *J. Amer. Chem. Soc.*, 1932, **54**, 4338; Burton, Shoppee, and Wilson, *J.*, 1932, 720) carried out the reactions (VI ⟶ V ⟶ VII) and did not detect any tendency for reaction as the rearranged form (VIII), although conversion into the acetate was not investigated. Roberts, Young, and Winstein (*J. Amer. Chem. Soc.*, 1942, **64**, 2157) found that 1- and

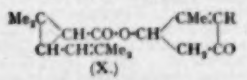
(VI.) (V.) (VII.) (VIII.)

3-methylallyl chlorides were converted by silver acetate in acetic acid, mainly by a S_N1 mechanism, into similar mixtures of acetates in which the primary acetate predominated. Subsequently Young and Andrews (*ibid.*, 1944, **66**, 421) found that on the alkaline hydrolysis in aqueous ethanol the primary chloride reacted mainly by a S_N2 mechanism to give predominantly the primary alcohol, whereas the secondary chloride reacted mainly by a S_N1 mechanism to give a mixed product. We consider that bromodihydrocinerone is predominantly (IIIa); this is consistent with the exclusive formation of (Id) on direct hydrolysis and with the deep-red colour of the 2 : 4-dinitrophenylhydrazone formed by bromotetrahydropyrethrone, indicative of αβ-unsaturation to the carbonyl group. Nevertheless the mechanism of the reaction with acetate ion, and presumably other carboxylate ions, is such that some (IIIb) could be present without detriment to the purity of the product.

Our main objective, the synthesis of racemic *dihydrocinerin*-I and *tetrahydropyrethrin*-I, was effected by refluxing bromodihydrocinerone and bromotetrahydropyrethrone respectively with silver (±)-*trans*-chrysanthemate (Campbell and Harper, *J.*, 1945, 283) in carbon tetra-



(IX.)



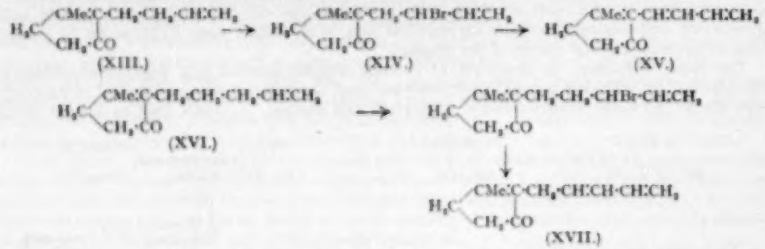
(X.)

		% Knock-down, 10 minutes' exposure.	% Kill, 24 hours.
(±)-n-Butylrethronyl (±)-*trans*-chrysanthemate (racemic dihydrocinerin-I)	(IX; R = Bu^n)	25	3·6
(±)-n-Butylrethronyl (±)-*cis*-chrysanthemate	(X; R = Bu^n)	15	3·8
(±)-n-Amylrethronyl (±)-*trans*-chrysanthemate (racemic tetrahydropyrethrin-I)	(IX; R = C_5H_{11}-n)	0	0·9
(±)-n-Amylrethronyl (±)-*cis*-chrysanthemate	(X; R = C_5H_{11}-n)	0	2·0
Official Test Insecticide	—	100 (in 3 mins.)	56·0 (mean of 3)
Odourless distillate alone	—	0	2·0
Unsprayed control	—	—	0·6 (mean of 6)

chloride. In a similar manner esters from (±)-*cis*-chrysanthemic acid (Campbell and Harper, *loc. cit.*) were prepared (see Table) (for an exposition of the nomenclature for these esters, see Harper, *Chem. and Ind.*, 1949, 636). These esters at a concentration of 0·5% w/v in refined kerosene ("odourless distillate" used as a spray base) have been tested for insecticidal activity against house-flies by Dr. E. A. Parkin and Mr. A. A. Green of the Insecticides Section, Pest Infestation Laboratory, with the results summarised in the Table. The values are those of a single spraying, using a 10-minutes' exposure in the spray chamber, by the standardised procedure of the Pest Infestation Laboratory (Parkin and Green, *Nature*, 1944, **154**, 16) and comparison is made with the Official Test Insecticide containing 0·1% w/v natural pyrethrins. Although the esters derived from dihydrocinerolone show slight knock-down, all give negligible kill. Such results are in accord with the low toxicity observed by Haller and Sullivan (*J. Econ. Entomol.*, 1938, **31**, 276) for hydrogenated natural pyrethrin-I, by Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 448) and by Gersdorff (*J. Econ. Entomol.*, 1947, **40**, 878) for (+)-*n*-amylrethronyl (+)-*trans*-chrysanthemate resynthesised from naturally derived acid and hydrogenated alcohol The double bonds in the side chains of the natural pyrethrins are therefore of great importance for insecticidal activity.

(XI.) (XII.)

Structures of the type of (XI) would be expected to eliminate HX with ease to give compounds which are formulated tentatively as *cyclo*pentadienones (XII) or their dimers. Thus Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 226) record that pyrethronyl acetate eliminates acetic acid on pyrolysis, and on distillation the pyrethrins themselves give a lower-boiling fraction. When the synthetic esters described above were distilled, a forerun of chrysanthemic acid was obtained and characterised as its *p*-phenylphenacyl ester. This was not due to the presence of free acid in the crude product since the silver salt would not have hydrolysed under the conditions of the reaction and prolonged heating of the silver salt in a vacuum gave no volatile product. Treatment of bromodihydrocinerone with anhydrous trimethylamine in benzene and warming the quaternary salt thus formed with an aqueous suspension of magnesium oxide eliminated 90% of the bromine as trimethylammonium bromide. The resulting *cyclo*pentadienone (XII; R = Bu^n) would be expected to exist in a dimeric form but yield monomeric derivatives. A *semicarbazone* (m. p. 227°) and a deep-red 2 : 4-*dinitrophenylhydrazone* were isolated in good yield and gave analytical values consitent with their being derivatives of 3-methyl-2-*n*-butyl*cyclo*penta-2 : 4-dien-1-one. Similarly bromotetrahydropyrethrone with methanolic sodium methoxide gave no methyl ether but 83% of the bromine was eliminated as hydrogen bromide to give a product yielding a *semicarbazone* (m. p. 219°), presumably of



3-methyl-2-*n*-amyl*cyclo*penta-2 : 4-dien-1-one. This semicarbazone is probably identical with that (m. p. 220°) which Staudinger and Ruzicka (*loc. cit.*) obtained from tetrahydropyrethrolone semicarbazone and regarded as being derived through heterocyclisation by elimination of water from the α-hydroxy-group.

Less success attended attempts to monobrominate, in the 4-position, *cyclo*pentenones related more closely to cinerone and pyrethrone in that they contained alkenyl side-chains. 3-Methyl-2-*n*-but-3′-enyl*cyclo*pent-2-en-1-one (XIII) reacted smoothly with one molecular proportion of *N*-bromosuccinimide, but after 15 minutes evolution of hydrogen bromide commenced. The sole product isolated by distillation was unchanged ketone (~15%) together with

a non-volatile polymeric residue. Evidently preferential substitution occurs at the 2′-methylene group adjacent to the side-chain double bond, together with some disubstitution, possibly at the 4-position. Elimination of hydrogen bromide from (XIV) would lead to a cross-conjugated trienone (XV) which might be expected to polymerise. Attention was then directed to 3-methyl-2-*n*-pent-4′-enylcyclopent-2-en-1-one (XVI) (the preparation of this ketone will be described in a forthcoming communication), for in this case preferential side-chain substitution at the 3′-position followed by elimination of hydrogen bromide could lead to pyrethrone (XVII) and thence, with substitution at the 4-position, possibly to pyrethrolone (Ia) itself. After reaction with one molecular proportion of *N*-bromosuccinimide (again hydrogen bromide was evolved), only unchanged ketone (48%) could be isolated: no monosubstitution occurred, but all the ketone that reacted underwent dibromination. On the assumption that any bromopyrethrone present might polymerise on distillation, the undistilled bromo-ketone was treated with silver acetate in glacial acetic acid and the product converted into the semicarbazone; again only the derivative of the starting ketone was obtained, with no indication of the presence of pyrethronyl acetate semicarbazone. The side-chain double bond was blocked by the addition of bromine and the product treated with *N*-bromosuccinimide, but reagents used to eliminate vicinal bromine atoms also attacked the labile bromine at position 4. The *N*-bromosuccinimide route is therefore incapable of extension to the preparation of ketols containing alkenyl side chains.

Experimental.

Microanalyses, other than bromine determinations, were carried out by Drs. Weiler and Strauss, Oxford.

Reaction of Dihydrocinerone with N-Bromosuccinimide.—Dihydrocinerone (3·19 g.) (regenerated from the semicarbazone; b. p. 113°/15 mm., n_D^{20} 1·4802; cf. Harper, *J.*, 1946, 892) and *N*-bromosuccinimide (3·75 g., 1·0 mol.) were heated to boiling in carbon tetrachloride (10 ml.). Reaction commenced, as shown by a marked increase in the rate of reflux and succinimide floating to the surface, within 5 to 10 minutes and was completed by a further 15—30-minutes' refluxing. In other experiments neither the addition of catalytic quantities of benzoyl peroxide nor the use of freshly recrystallised *N*-bromosuccinimide caused any significant variation. The suspension was cooled to 0° and the succinimide collected (2·09 g., 99·5%). The carbon tetrachloride was removed from the filtrate by distillation through a short column at atmospheric pressure and the residue kept over paraffin wax in a vacuum desiccator, to give the crude bromo-ketone (5·52 g., 98%), n_D^{20} 1·5177. In another experiment the crude bromo-ketone (4·08 g.) was distilled at *ca.* 5×10^{-3} mm. through a plain column (220 × 6 mm.), both the flask and column being immersed in an oil-bath, to give the fractions: (i) b. p. 42—46° (0·21 g.); (ii) b. p. 47—56°, n_D^{20} 1·5132 (0·78 g.); (iii) b. p. 56—63°, n_D^{20} 1·5193 (1·69 g.) (Found: Br, 33·9. $C_{10}H_{11}OBr$ requires Br, 34·6%); (iv) b. p. 63—70° (0·62 g.); and (v) b. p. 85—88° (0·44 g.) (Found: Br, 45·4. $C_{10}H_{10}OBr_2$ requires Br, 51·5%). Fraction (i) consisted of unchanged ketone and the recovery of this together with the quantitative recovery of succinimide is consistent with the presence of dibromodihydrocinerone in (v). The spread of b. p. of fractions (ii)—(iv) of the *monobromodihydrocinerone* was caused, in part at least, by fluctuation of pressure but does not entirely exclude heterogeneity of the product.

Hydrolysis of Bromodihydrocinerone.—In early experiments, carried out in 1946, direct hydrolysis of the undistilled bromo-ketone was attempted by refluxing it with aqueous potassium carbonate. This procedure yielded a bromine-free product, boiling in the correct range for dihydrocinerolone, which it was attempted to characterise as semicarbazone. However, only small quantities of impure derivative were obtained which could not be satisfactorily purified. Later experience showed that even when pure ketol is used the semicarbazone is formed and isolated with difficulty and only in low yield. It is likely therefore that (±)-dihydrocinerolone was actually obtained in these experiments.

The undistilled bromo-ketone (4·50 g.) and powdered silver acetate (7·5 g.) were refluxed in glacial acetic acid (25 ml.) for 4 hours. Next day the silver bromide was filtered off (3·08 g., after being washed with dilute nitric acid, equiv. to only 83·5% reaction) and the acetic acid removed by distillation through a short column under slightly reduced pressure. Distillation of the residue yielded, after a small forerun, *acetoxydihydrocinerone* [*(±)-dihydrocinerolyl acetate*] (2·47 g., 60%), b. p. 100—103° (mainly 101°)/0·75 mm., n_D^{20} 1·4772 (Found: C, 68·2; H, 9·2. $C_{11}H_{18}O_3$ requires C, 68·2; H, 8·6%). The semicarbazone, prepared in the cold, had m. p. 148° not clearing until 163°, but could not be satisfactorily purified. The red 2 : 4-dinitrophenylhydrazone when prepared in cold alcoholic hydrochloric acid and crystallised from methanol had m p. 125—126°, but when prepared in boiling alcoholic hydrochloric acid and crystallised from ethanol or Cellosolve (methyl ether) had m. p. 136—137°. In another experiment, with 2·60 g. of undistilled bromo-ketone, the product was fractionally distilled at 0·3 mm. to give the fractions: (i) b. p. 63—69°, n_D^{20} 1·4810 (80 mg.) (Found: C, 75·9; H, 10·5. Calc. for $C_{10}H_{14}O$: C, 78·9; H, 10·6%); (ii) b. p. 87—88°, n_D^{20} 1·4770 (760 mg.) (Found: C, 68·6; H, 8·9. $C_{11}H_{18}O_3$ requires C, 68·2; H, 8·6%); (iii) b. p. 89—92°, n_D^{20} 1·4775 (180 mg.) (Found: C, 68·2; H, 8·5%); (iv) b. p. 95°, n_D^{20} 1·4778 (310 mg.); and (v) b. p. 129—131° (210 mg.) (Found: C, 65·4; H, 8·2. $C_{14}H_{20}O_5$ requires C, 62·6; H, 7·5%). Fraction (i) contained unchanged ketone which it was shown above is present in undistilled bromo-ketone. Fractions (ii)—(iv) consisted of the *monoacetoxy-ketone*, there being no indication of heterogeneity. Fraction (v) contained *diacetoxydihydrocinerone* derived from the small proportion of dibromoketone formed in the initial substitution.

Acetoxydihydrocinerone (1·63 g.) was hydrolysed by being refluxed with excess of 0·5*N*-methanolic potassium hydroxide and following the course of the reaction by back-titration at 20-minute intervals.

After 60 minutes hydrolysis was 95% complete and the methanol was removed through a column. Ether-extraction of the oily suspension, drying, and distillation yielded, after a small forerun, (±)-dihydrocinerolone (0·95 g., 73%), b. p. 114—117°/0·8 mm., n_D^{20} 1·4942; Soloway and LaForge (*J. Amer. Chem. Soc.*, 1947, **69**, 979) record b. p. 110—114°/0·3 mm., n_D^{20} 1·4955, for their synthetic ketol; LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 222) record b. p. 115—117°/1 mm., n_D^{20} 1·4958, for "natural" material. The **3**: 5-dinitrobenzoate, triturated with light petroleum and crystallised twice from ethanol, had m. p. 110—110·5° (Found: C, 56·3; H, 5·0. Calc. for $C_{17}H_{18}O_8N_2$: C, 55·5; H, 4·9%); Soloway and LaForge (*loc. cit.*) record m. p. 111° for their synthetic derivative and m. p. 111° for the "natural" ester. The semicarbazone had m. p. 184—185°; Soloway and LaForge (*loc. cit.*) record m. p. 187° for their synthetic derivative; LaForge and Barthel (*loc. cit.*) record m. p. 185°; and West (*J.*, 1946, 463) records 184—185° for the naturally derived (±)-semicarbazone.

Reaction of Tetrahydropyrethrone with N-Bromosuccinimide.—Tetrahydropyrethrone (4·47 g.) (regenerated from the semicarbazone; b. p. 82·5°/0·7 mm., n_D^{20} 1·4764) was brominated, by the above procedure, to give the crude bromo-ketone (6·6 g.) (**2**: 4-dinitrophenylhydrazone, deep-red needles, m. p. 128—130°, from methanol).

Hydrolysis of Bromotetrahydropyrethrone.—The undistilled bromo-ketone (6·6 g.) was likewise treated with silver acetate (12·0 g.) in boiling glacial acetic acid (25 ml.), and the product fractionally distilled at 3 mm. to give the fractions: (i) b. p. 116·5—124°, n_D^{20} 1·4731 (0·24 g.); (ii) b. p. 124—129°, n_D^{20} 1·4755, (0·22 g.); (iii) b. p. 129—135°, n_D^{20} 1·4764 (0·33 g.); (iv) b. p. 135—140°, n_D^{20} 1·4750 (1·00 g.); (v) b. p. 140—144°, n_D^{20} 1·4745 (1·67 g.); (vi) b. p. 144—148°, n_D^{20} 1·4750 (0·86 g.); and (vii) b. p. 148—168°, n_D^{20} 1·4770 (0·38 g.). Fractions (iv)—(vi) were bulked and redistilled to give acetoxytetrahydropyrethrone [(±)-tetrahydropyrethronyl acetate] (3·01 g., 50% overall yield from tetrahydropyrethrone), b. p. 144—146°/3 mm., n_D^{20} 1·4747 (Found: C, 69·6; H, 9·5. Calc. for $C_{12}H_{20}O_3$: C, 69·6; H, 9·0%). Dauben and Wenkert (*J. Amer. Chem. Soc.*, 1947, **69**, 2075) record b. p. 120—123°/1 mm., n_D^{20} 1·4755, for their synthetic product; West (*J.*, 1945, 412) records b. p. 117°/1·3 mm., n_D^{20} 1·4761, for naturally derived (+)-acetate.

In another experiment, in an attempt to eliminate some of the manipulation, tetrahydropyrethrone (1·72 g.) was brominated with *N*-bromosuccinimide (1·85 g.) in carbon tetrachloride (15 ml.) and the separated succinimide filtered off. Silver acetate (1·0 g.) was added to the filtrate, and the suspension shaken at room temperature for 48 hours. After filtration and removal of the solvent the residue was fractionally distilled at 0·4 mm. to give the fractions: (i) b. p. 78—80°, n_D^{20} 1·4804 (120 mg.) (Found: C, 75·7; H, 10·0. Calc. for $C_{11}H_{18}O$: C, 79·4; H, 10·9%); (ii) b. p. 91—103°, n_D^{20} 1·4808 (150 mg.); (iii) b. p. 103°, n_D^{20} 1·4796 (260 mg.) (Found: C, 68·6; H, 9·0. Calc. for $C_{12}H_{20}O_3$: C, 69·6; H, 9·0%); (iv) b. p. 104°, n_D^{20} 1·4797 (130 mg.); and (v) b. p. 105°, n_D^{20} 1·4804 (140 mg.) (Found: C, 68·7; H, 9·15%). Fractions (i)—(ii) evidently contained unreacted tetrahydropyrethrone; fractions (iii)—(v) were pure acetoxytetrahydropyrethrone.

Although the acetoxy-ketone gave a deep-red **2**: 4-dinitrophenylhydrazone this could not be satisfactorily purified. The semicarbazone, which separated as an oil and only slowly solidified, had m. p. 132—132·5°, but there was insufficient for purification; Dauben and Wenkert (*loc. cit.*) record m. p. 85—86° for the semicarbazone, but this seems far too low, particularly as the naturally derived (+)-semicarbazone has m. p. 140—141° (West, *loc. cit.*).

In an attempt to hydrolyse acetoxytetrahydropyrethrone, the ester was recovered unchanged after 24 hours' refluxing with an aqueous-alcoholic suspension of barium carbonate. However, hydrolysis was achieved by refluxing the acetoxy-ketone (0·63 g.) with a slight excess of 0·5*N*-methanolic potassium hydroxide for 1 hour. Extraction and distillation gave, after a small forerun, (±)-tetrahydropyrethrolone (0·25 g., 49%), b. p. 125—127°/0·4 mm., n_D^{20} 1·4882 (Found: C, 72·1; H, 9·9. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 10·0%); Dauben and Wenkert (*loc. cit.*) record b. p. 118—120°/0·3 mm., n_D^{25} 1·4921 for their synthetic ketol; West (*loc. cit.*) records b. p. 126—127°/0·8 mm., n_D^{20} 1·4932, for naturally derived (+)-ketol; LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 114) record n_D^{20} 1·4900 and for (+)-tetrahydropyrethrolone, n_D^{20} 1·4892. The **3**: 5-dinitrobenzoate crystallised as needles with m. p. 103—106°; Dauben and Wenkert (*loc. cit.*) record m. p. 105—105·5° for the synthetic ester. The semicarbazone, crystallised from ethyl acetate, had m. p. 169°; Dauben and Wenkert (*loc. cit.*) record m. p. 170·2—170·6° for the synthetic semicarbazone; LaForge and Barthel (*loc. cit.*) record m. p. 172—173° and West (*J.*, 1946, 463) records m. p. 172—174° for the "natural" (±)-semicarbazone.

Preparation of Pyrethrins.—The (±)-*trans*-chrysanthemic acid used was prepared by Mr. H. W. B. Reed following the procedure of Campbell and Harper (*J.*, 1945, 283). When freshly prepared it had m. p. 54·0—54·5°, but when kept developed an unpleasant odour and softened before melting. This is characteristic of the *trans*-acid, whereas the (±)-*cis*-acid remains unchanged over a period of years. The (±)-*trans*-acid (2·02 g.) in alcohol was neutralised with approx. 0·1*N*-potassium hydroxide (phenolphthalein) and then rendered faintly acid with dilute nitric acid, a slight excess of aqueous ammonia added, and the solution boiled until neutral. The silver salt was precipitated with a slight excess of approx. 0·1*N*-silver nitrate, washed, and dried at 100° to a grey powder (3·02 g., 92%).

Silver (±)-*trans*-chrysanthemate (2·83 g., 1·1 mols.) was added to the filtered solution of bromodihydrocinerone in carbon tetrachloride (25 ml.), freshly prepared from dihydrocinerone (1·45 g.). The reaction mixture was kept at room temperature overnight, then refluxed for 30 minutes, filtered, and evaporated, and the residue was distilled at 10^{-2} mm. in a small flask with a short distillation path. The following fractions were obtained: (i) b. p. 65—72° (660 mg.); (ii) b. p. 105—121° (880 mg.); and (iii) b. p. 121—130° (580 mg.). Fraction (iii) was yellow because of decomposition towards the end of the distillation. Redistillation of fractions (ii) and (iii), after a small forerun, yielded (±)-n-*butylrethronyl* (±)-trans-*chrysanthemate* (*dihydrocinerin*-I), b. p. 114—115°/1 × 10^{-2} mm., n_D^{20} 1·4992 (890 mg., 29% overall) (Found: C, 74·75; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·5; H, 9·5%). An attempt to characterise this keto-ester as a 4-phenylsemicarbazone failed. When fraction (i) was cooled to −80°, crystallisation started. The solid had m. p. 42—52° (Found: C, 71·1; H, 9·4. Calc. for $C_{10}H_{14}O_2$: C, 71·4; H, 9·6%). Its identity as (±)-*trans*-chrysanthemic acid was confirmed by preparation of the *p*-phenylphenacyl ester, m. p. 113·5—115°, not depressed on admixture with an authentic specimen (Campbell and Harper, *loc. cit.*). Although silver (±)-*trans*-chrysanthemate became black and formed a mirror when heated to

240° at 10^{-4} mm., no distillation occurred. It is evident that the acid obtained above was formed by pyrolysis of the ester.

Tetrahydropyrethrin-I was prepared similarly by bromination of tetrahydropyrethrone (1·0 g.) and reaction with silver (±)-*trans*-chrysanthemate (1·90 g.). Fractional distillation of the crude product at 10^{-3} mm. gave (i) b. p. 56—57° (440 mg.) (Found: C, 71·0; H, 9·55. Calc. for $C_{20}H_{34}O_4$: C, 71·4: H, 9·6%), and (ii) b. p. 110—150° (770 mg.). Fraction (i) crystallised and was evidently (±)-*trans*-chrysanthemic acid. Redistillation of fraction (ii) with elimination of a small forerun (50 mg.), yielded (±)-n-*amylrethronyl* (±)-trans-*chrysanthemate* (*tetrahydropyrethrin-I*), b. p. 96°/7 × 10^{-4} mm., n_D^{25} 1·4970 (410 mg., 21% overall) (Found: C, 74·2; H, 9·6. $C_{21}H_{36}O_3$ requires C, 75·9; H, 9·7%). The keto-ester gave a brick-red 2 : 4-dinitrophenylhydrazone crystallising after many recrystallisations from ethanol, as prisms, m. p. 167°.

(±)-*cis*-Chrysanthemic acid (1·02 g.) was dissolved in a slight excess of 2·5N-sodium hydroxide, and rendered slightly acid with dilute nitric acid and then just alkaline with ammonia. The silver salt was precipitated by a slight excess of approx. 0·1N-silver nitrate, washed, and dried at 100° (1·41 g., 87%).

By a similar procedure dihydrocinerone (700 mg.) was brominated and then treated with silver (±)-*cis*-chrysanthemate (1·18 g.). The product boiled mainly at 133—144°/3 × 10^{-3} mm., and crystals of (±)-*cis*-chrysanthemic acid separated on storage. A light-petroleum solution was therefore washed with sodium hydrogen carbonate, and the residual ester re-distilled, to give (±)-n-*butylrethronyl* (±)-*cis*-*chrysanthemate*, b. p. 117—119°/3 × 10^{-3} mm., n_D^{25} 1·5000 (580 mg., 38% overall) (Found: C, 74·1, 74·2; H, 9·6, 9·5. $C_{20}H_{34}O_3$ requires C, 75·5; H, 9·5%).

Tetrahydropyrethrone (740 mg.) was brominated and then treated with silver (±)-*cis*-chrysanthemate (1·28 g.). Distillation at 10^{-3} mm. gave fractions: (i) b. p. 63—95° (40 mg.), and (ii) b. p. 120—153° (900 mg.). Both fractions deposited crystals when kept, which after being rinsed with light petroleum had m. p. 109—113°, not depressed on admixture with authentic (±)-*cis*-chrysanthemic acid. The light-petroleum solution was washed with sodium hydrogen carbonate, dried, evaporated, and distilled, to give (±)-n-*amylrethronyl* (±)-cis-*chrysanthemate*, b. p. 120—124°/2 × 10^{-4} mm., n_D^{25} 1·4980 (640 mg., 43% overall) (Found: C, 74·9; H, 9·6. $C_{21}H_{36}O_3$ requires C, 75·9; H, 9·5%).

Immediately after distillation portions of these esters were sealed under nitrogen for analysis and for insecticidal assay. Portions kept for nearly 2 years show no signs of deterioration.

Elimination of Hydrogen Bromide from Bromodihydrocinerone.—Anhydrous trimethylamine vapour was passed into a solution of the bromo-ketone (850 mg.; b. p. 86°/6 × 10^{-4} mm., n_D^{25} 1·5178) in dry thiophen-free benzene (10 ml.). There was an immediate precipitate of white crystals. The suspension was kept for 12 hours, and then more trimethylamine vapour was passed in to complete the reaction. Benzene was removed in a vacuum at 40°, a suspension of magnesium oxide (400 mg.) in a little water was added, and the suspension boiled for 30 minutes. The organic material was extracted with ether, and the extract divided into two portions after being dried. One portion of the ethereal extract was evaporated and the residue converted into the 2 : 4-*dinitrophenylhydrazone* in boiling alcoholic hydrochloric acid. It separated in two forms from Cellosolve (methyl ether)—a dark red form crystallising almost at once and an orange modification which separated only on long storage of the mother-liquor. Both formed dark red blades, m. p. 236°, from alcohol–nitrobenzene (Found: C, 58·75; H, 5·4; N, 16·6. $C_{16}H_{18}O_5N_4$ requires C, 58·2; H, 5·5; N, 16·95%). The other portion of the extract yielded, after 5 minutes' refluxing with semicarbazide hydrochloride in pyridine–ethanol solution, a semicarbazone, m. p. 227° (decomp.) (from Cellosolve) (Found: C, 63·1; H, 8·0. $C_{11}H_{17}ON_3$ requires C, 63·7; H, 8·3%). Attempts to characterise the 3-methyl-2-n-butylcyclopenta-2 : 4-dien-1-one as its dimer were unsuccessful.

Elimination of Hydrogen Bromide from Bromotetrahydropyrethrone.—Undistilled bromo-ketone (500 mg.) was added to a cold solution of sodium (47 mg., 1 g.-atom) in methanol (5 ml.) and kept for 12 hours at room temperature. The orange solution was acidified and extracted with ether. The ethereal extract was evaporated and the residue converted into the *semicarbazone*, which formed microcrystalline needles (from Cellosolve), m. p. 219° (Found: C, 65·0; H, 8·95; N, 18·1. $C_{15}H_{25}ON_3$ requires C, 65·1; H, 8·65; N, 19·0%), and was evidently the derivative of 3-methyl-2-n-amylcyclopenta-2 : 4-dien-1-one and not the methyl ether semicarbazone ($C_{16}H_{27}ON_3$ requires C, 61·6; H, 9·15; N, 16·5%)

Undistilled bromo-ketone (from 197 mg. of tetrahydropyrethrone) was refluxed with zinc dust (160 mg.) in ethanol (2 ml.) for 45 minutes. Addition of water and extraction with ether yielded a viscous product which was converted into the semicarbazone. This derivative separated quickly and after recrystallisation from Cellosolve had m. p. 221—223° not depressed on admixture with the above semicarbazone, m. p. 219°. Evidently elimination of hydrogen bromide occurred instead of reductive replacement of bromine to give tetrahydropyrethrone (semicarbazone, m. p. 177°), although LaForge and Haller (*J. Org. Chem.*, 1936, **1**, 38) were able to reduce chlorotetrahydropyrethrone to tetrahydropyrethrone by this method.

The bromo-ketone liberated iodine from potassium iodide in boiling ethanol.

Reaction of 3-*Methyl*-2-n-*but*-3′-*enylcyclopent*-2-*en*-1-*one with* N-*Bromosuccinimide.*—The ketone (1·20 g.) (regenerated from the semicarbazone; b. p. 129—133°/25 mm., n_D^{25} 1·4928; cf. Harper, *loc. cit.*) reacted smoothly with *N*-bromosuccinimide (1·42 g., 1·0 mol.) in boiling carbon tetrachloride (30 ml.). After 15 minutes evolution of hydrogen bromide was observed, and refluxing was continued until this was complete (*ca.* 1 hour). After filtration and evaporation of the solvent the viscous residue was distilled. The sole volatile product (160 mg.) had b. p. 50°/7 × 10^{-3} mm. and gave a 2 : 4-dinitrophenylhydrazone, crystallising from ethanol in red needles, m. p. 145°, not depressed on admixture with the 2 : 4-dinitrophenylhydrazone of the original ketone (Harper, *loc. cit.*). This derivative occasionally exhibits dimorphism, having then m. p. *ca.* 160°.

Reaction of 3-*Methyl*-2-n-*pent*-4′-*enylcyclopent*-2-*en*-1-*one with* N-*Bromosuccinimide.*—The ketone (1·64 g.) (regenerated from the semicarbazone; b. p. 127—129°/20 mm., n_D^{25} 1·4948) reacted with *N*-bromosuccinimide (1·78 g., 1·0 mol.) in warm carbon tetrachloride (10 ml.). Refluxing was continued until the evolution of hydrogen bromide commenced. The suspension was then quickly cooled, filtered (0·91 g. of succinimide, 88%), and evaporated. Distillation of the residue gave, as the sole volatile

product, unchanged ketone, b. p. 82—91°/0·35 mm., n_D^{20} 1·4997 (0·95 g.), and a polymeric residue. The distillate was converted into the semicarbazone (1·07 g., 48%), which had m. p. 172—173° after one crystallisation and did not depress the m. p. of the original ketone semicarbazone. The ketone reacted with 2 molecular proportions of *N*-bromosuccinimide but required the addition of benzoyl peroxide after 30 minutes' refluxing to complete the reaction.

In another experiment refluxing was continued until evolution of hydrogen bromide was complete. Without distillation the product was refluxed with silver acetate in glacial acetic acid. The suspension was filtered, the acetic acid removed in a vacuum, and the residue converted directly into the semicarbazone. The product had, however, m. p. 171—172° which was not depressed on admixture with the semicarbazone of the original ketone.

Addition of 10% bromine in carbon tetrachloride (1 mol.) to the ketone below 0° required illumination for decolorisation to occur. The 3-methyl-2-(4′ : 5′-dibromo-*n*-amyl)*cyclo*pent-2-en-1-one so formed was characterised by a 2 : 4-*dinitrophenylhydrazone*, m. p. 123—124° (Found: C, 41·3; H, 3·8. $C_{17}H_{20}O_4N_4Br_2$ requires C, 40·5; H, 4·0%). Without isolation the dibromo-ketone was treated with *N*-bromosuccinimide (1 mol.); reaction took place rapidly, with some evolution of hydrogen bromide towards the end. Refluxing of the tribromo-ketone with potassium iodide in ethanol effected only partial removal of the vicinal bromine atoms. This was confirmed by re-examination of the dibromo-ketone which likewise reacted only slightly with potassium iodide in ethanol.

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UNIVERSITY COLLEGE, SOUTHAMPTON.
KING'S COLLEGE (UNIVERSITY OF LONDON), STRAND, W.C.2. [*Received, January 3rd*, 1950.]

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201. *Some Compounds related to the Aromatic "Nitrogen Mustards."*

By GEORGE A. R. KON and JOHN J. ROBERTS.

The preparation of certain compounds related to the cytotoxic "nitrogen mustards" is described.

NUMEROUS di(halogenoalkyl)arylamines, of which di-(2-chloroethyl)aniline $Ph{\cdot}N(CH_2{\cdot}CH_2Cl)_2$ is typical, have been found to have a powerful cytotoxic activity and to inhibit the growth of transplanted tumours in rats (Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824). A number of such compounds has been described (Ross, *J.*, 1949, 183; Everett and Ross, *ibid.*, p. 1972) and certain generalisations have been made in relating the structure of the compounds to their biological activity. Thus, it appears essential that two halogenoalkyl chains should be present and that the halogen atoms should not be separated from the nitrogen by more than two carbon atoms; the activity of these compounds could be satisfactorily related to the ease of hydrolysis of the halogen atoms in aqueous acetone.

It appeared of interest to test these conclusions by examining related compounds possessing two side chains of unequal length, and also compounds with side chains longer than the optimum but with additional substituents conferring the requisite reactivity on the halogen atoms.

For this purpose a series of anilino-alcohols was prepared. These call for little comment, except that 4-anilinobutanol, which had already been obtained (Ross and Everett, *loc. cit.*), has now been prepared more easily in a pure state by condensing aniline with 4-chlorobutyl acetate to give the crystalline *4-anilinobutyl acetate*, which was then hydrolysed. The latter acetate could also be condensed with a second molecule of chlorobutyl acetate to give *di-*(*4-acetoxybutyl*)-*aniline*, and the parent compound was obtained in a pure state by alkaline hydrolysis; however, all attempts to prepare the corresponding chloro-derivative failed.

Condensation of the anilino-alcohols with ethylene chlorohydrin afforded compounds of the type $Ph{\cdot}N(CH_2{\cdot}CH_2{\cdot}OH){\cdot}[CH_2]_n{\cdot}OH$, where n was 2, 3, 4, and 5, and the products were then converted into the chlorides. Attempts to prepare the same compounds with the aid of ethylene oxide were not successful. Similar compounds were obtained when using 3-chloropropyl alcohol in place of ethylene chlorohydrin, but the series was not extended further because compounds with longer side chains were invariably inactive, in agreement with their low rate of hydrolysis in aqueous acetone.

This inactivity was not due purely to steric factors such as the separation of the reacting groups in space owing to lengthening of the side chain; this was strikingly borne out by an examination of a series of compounds of the general type (I), in which the terminal halogen

atoms can be more widely separated, for reactivity depends on their position with reference to the activating group, namely nitrogen.

$$\begin{matrix} ArN\text{—}[CH_2]_m\text{—}NAr \\ [CH_2]_n\text{·Hal} \quad [CH_2]_n\text{·Hal} \end{matrix} \qquad (I.)$$

For the preparation of compounds in which the nitrogen atoms are separated by two or more carbon atoms two methods are available and both have been used: in one of these two molecules of the anilino-alcohol are condensed with one of the appropriate alkylene dibromide, a method already much used by von Braun in analogous cases (*Ber.*, 1908, **41**, 2156):

$$2Ph\cdot NH\cdot[CH_2]_n\cdot OH + Br\cdot[CH_2]_m\cdot Br \longrightarrow \begin{matrix} PhN\text{—}[CH_2]_m\text{—}NPh \\ [CH_2]_n\cdot OH \quad [CH_2]_n\cdot OH \end{matrix}$$

alternatively, an αω-dianilinoalkane is condensed with ethylene oxide or a chlorohydrin:

$$Ph\cdot NH\cdot[CH_2]_m\cdot NHPh \longrightarrow \begin{matrix} PhN\text{—}[CH_2]_m\text{—}NPh \\ [CH_2]_2\cdot OH \quad [CH_2]_2\cdot OH \end{matrix}$$

Chlorination of the hydroxyl groups then affords the appropriate chloro-compound. The second method appeared to be especially promising as a route to compounds in which $m = 1$, since Eibner has described the preparation of di-(*o*-tolyl)methane and other similar compounds (*Annalen*, 1898, **302**, 349). This compound was condensed with ethylene chlorohydrin to give a product which appeared to be mainly the desired dihydroxyethyl derivative, but it could not be completely purified and gave no definite compound on chlorination.

It was hoped to obtain similar compounds by a variant of the first method, namely by condensing anilino-alcohols with formaldehyde. The condensation of some ethanolamines with formaldehyde, acetaldehyde, and benzaldehyde has been studied by Knorr and Matthes (*Ber.*, 1901, **34**, 3484), who showed that the intermediate compounds lose water and cyclise to oxazolidines:

$$RNH\cdot CH_2\cdot CH_2\cdot OH + CH_2O \longrightarrow \left[RN\begin{matrix} CH_2\cdot CH_2\cdot OH \\ CH_2\cdot OH \end{matrix} \right] \longrightarrow RN\begin{matrix} CH_2\text{—}CH_2 \\ CH_2\text{—}O \end{matrix}$$

Bergmann, Ulpts, and Camacho (*ibid.*, 1922, **55**, 2706) found that phenetidinoethanol behaved similarly. We have prepared a number of *N*-aryloxazolidines in the same way. 3-Anilinopropanol also condensed readily with formaldehyde to afford *3-phenyl-1:3-oxazine*. 4-Anilinobutanol gave under similar conditions what appeared to be the intermediate hydroxymethyl compound, which was unstable and lost water on distillation to pass into the cyclic compound, *3-phenyl-1:3-pentoxazoline* (*3-phenyl-1-oxa-3-azacycloheptane*). *5-Anilinopentanol* and *6-anilinohexanol* appeared to react with formaldehyde, but on distillation the products decomposed and the starting materials were the only products isolated. All efforts to condense esters of anilino-alcohols with formaldehyde and so avoid cyclisation were fruitless.

The preparation of compounds in which the nitrogen atoms are more widely separated did not present much difficulty; the compounds of type (I) in which $n = m = 2$ were some of the most active compounds yet tested and this has prompted the preparation of several analogues, in which the group Ar and the side-chain were varied. It may be noted that aliphatic analogues of these, such as *NN'*-diethyl-*NN'*-di-(2-chloroethyl)ethylenediamine, have proved to be active cytotoxic agents (SK 882, Abstract of Final Report to the Chemical Corps, March 14th, 1948).

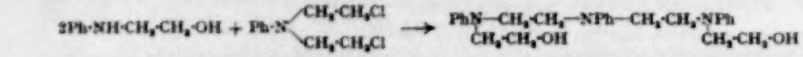
Biological activity is maintained in derivatives of propylenediamine and gradually falls off as the distance between the nitrogen atoms is increased. Lengthening of the halogenoalkyl side chains, on the other hand, leads to complete loss of activity, in agreement with the theoretical views developed above. Thus, already the di-3-chloropropyl derivative of *NN'*-diphenylethylenediamine is inactive.

To afford a comparison with the compounds already described by Ross (*loc. cit.*) a few representative compounds of type (I) have been hydrolysed in boiling 50% acetone–water for ½ hour and the following values obtained:

Ar.	*m*.	*n*.	% Hydrolysed.	Ar.	*m*.	*n*.	% Hydrolysed.
Ph	2	2	33	1-$C_{10}H_7$	2	2	67
Ph	3	2	40	2-$C_{10}H_7$	2	2	18
Ph	4	2	45	*p*-OMe-C_6H_4 ...	2	2	55
Ph	5	2	44	Ph	2	3	<1
Ph	6	2	54	Ph	2	*	83

* Side chain = ·CH_2·CHMeCl.

Interesting analogues of these compounds should be formed by the condensation of 2 moles of anilinoethanol with one of a di(halogenoalkyl)aniline:



Unfortunately all attempts to prepare such compounds led to diarylpiperazines (cf. Davis and Ross, *J.*, 1949, 2831).

Experimental.

(M. p.s are uncorrected.)

Arylamino-alcohols.—2-Anilinoethanol was prepared as described by Schorygin and Smirnov (*J. Gen. Chem. Russia*, 1934, **4**, 830). 3-Anilinopropanol, which had previously been obtained in 29% yield by condensing allyl alcohol with aniline (Hromatka, *Ber.*, 1942, **75**, 379), has now been obtained in 70% yield from trimethylene chlorohydrin and aniline by Schorygin and Smirnov's procedure, namely by dropping the chlorohydrin (1 mol.) during ½ hour into aniline (2 mols.) and water (1 mol.) kept at about 140° and then gently boiling the mixture for 1 hour; alkali was added to the cooled product and the anilino-alcohol extracted with ether and purified by distillation. 2-Anilinopropanol (Dains, Joss, and Stubbs, *Univ. Kansas Sci. Bull.*, 1931, **20**, 161) was conveniently prepared by heating equimolecular quantities of aniline and propylene oxide to 150° for 15 hours and then working up the product as above (yield 70%). 4-Chlorobutyl acetate (Cloke and Pilgrim, *J. Amer. Chem. Soc.*, 1939, **61**, 2667) (0·1 mol.) was boiled under reflux with aniline (0·1 mol.), calcium carbonate (0·05 mol.), and water (50 c.c.) for 10 hours, with vigorous stirring; the product, isolated by means of ether, gave on distillation 25% of a fraction, b. p. 150—155°/1·8 mm., which solidified and then crystallised from pentane in plates, m. p. 33—34°, consisting of *4-anilinobutyl acetate* (Found: C, 69·8; H, 8·7. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·3%). The alcohol was obtained from the acetate by hydrolysis with cold methanolic potassium hydroxide and boiled at 138—140°/1 mm. (Found: C, 72·5; H, 9·2. Calc. for $C_{10}H_{13}ON$: C, 72·7; H, 9·2%). Pentamethylene chlorohydrin (Bennett and Heathcote, *J.*, 1929, 268) was boiled with 2 moles of aniline for 6 hours; excess of aqueous potassium hydroxide was added to the cooled product, which was extracted with ether, giving 45% of *5-anilinopentanol*, b. p. 164°/1·4 mm. (Found: C, 73·7; H, 9·7. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6%). Hexamethylene chlorohydrin (Müller and Vanc, *Monatsh.*, 1947, **77**, 259) gave on similar treatment a 74% yield of *6-anilinohexanol*, b. p. 138°/0·05 mm., crystallising as stout needles, m. p. 42°, from benzene–light petroleum (Found: C, 74·5; H, 10·0. $C_{12}H_{19}ON$ requires C, 74·5; H, 9·9%). When 2-naphthylamine was heated with ethylene chlorohydrin with or without the addition of chalk and water, *2-naphthylaminoethanol* could not be isolated from the product; it was, however, formed together with the *NN*-bishydroxyethyl compound (Ross, *loc cit.*) on heating naphthylamine with one mole of ethylene oxide to 100° for 6 hours; the crude reaction product was freed from unchanged naphthylamine and some dinaphthylamine by chromatography in benzene solution on Spence type H alumina; the hydroxylated compounds were recovered by stripping the column with methanol; they were treated with formaldehyde (see below), and the *oxazolidine* formed was separated by chromatography in ethereal solution and recovered from the first runnings; it formed plates, m. p. 91—92°, from methanol (Found: C, 78·3; H, 6·6. $C_{15}H_{15}ON$ requires C, 78·4; H, 6·6%). The oxazolidine (5 g.) was dissolved in the minimum amount of alcohol, and 10 c.c. of hydrochloric acid were added, causing a deep red colour to develop. The solution was heated to the b. p., rapidly cooled, diluted, basified, and extracted with ether. The ethereal extract gave a good yield of 2-naphthylaminoethanol, b. p. ~180°/0·7 mm., m. p. 49—50° (crystallised after being rubbed with light petroleum) (Found: C, 76·5; H, 7·0%. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0%). The compound rapidly darkens on exposure to light and air and is therefore difficult to crystallise although a small amount of prisms has been obtained by slow evaporation of a benzene–light petroleum solution.

N-2-Hydroxyethyl-N-3′-hydroxypropylaniline, obtained from 3-anilinopropanol and ethylene chlorohydrin in 75% yield as described for anilinobutyl acetate, had b. p. 180—190°/0·3 mm. (Found: C, 67·7; H, 8·8. $C_{11}H_{17}O_2N$ requires C, 67·7; H, 8·8%).

N-2-Chloroethyl-*N*-3′-chloropropylaniline was prepared from the preceding compound by the general method given by Everett and Ross (*loc. cit.*) and was a pale yellow oil, which was analysed in the form of its *picrate*, yellow plates, m. p. 91° (Found: N, 12·7. $C_{17}H_{16}O_7N_4Cl_2$ requires N, 12·3%). The yield was 50%; the same method of chlorination was used throughout this work and gave yields varying from 40 to 60%.

N-2-Hydroxyethyl-N-4′-hydroxybutylaniline, obtained from anilinobutanol in 76% yield as described for the previous compound, had b. p. 180—190°/0·4 mm. (Found: C, 69·1; H, 9·5. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·2%).

N-2-Chloroethyl-*N*-4′-chlorobutylaniline was an oil which was analysed in the form of its *picrate*, yellow plates, m. p. 103—104° (Found: C, 45·9; H, 4·5. $C_{18}H_{18}O_7N_4Cl_2$ requires C, 45·5; H, 4·2%). When kept, the chloro-compound gradually deposited a solid, m. p. 174°. Titration with silver nitrate and dichlorofluorescein suggested that one chlorine had become ionic and the compound was probably *N*-phenyl-*N*-2-chloroethylpyrrolidinium chloride.

NN-Di-(4-hydroxybutyl)anilines. Equimolecular quantities of 4-anilinobutyl acetate and 4-chlorobutyl acetate were condensed as described under the preparation of the former compound (20 hours). The fraction, b. p. 190—210°/0·3 mm. (20% yield), was the *diacetate* (Found: C, 67·2; H, 8·3. $C_{18}H_{27}O_4N$ requires C, 67·3; H, 8·5%) from which the required alcohol was obtained on hydrolysis with cold methanolic potassium hydroxide; the *diol* had b. p. 190°/0·3 mm. (Found C, 70·7; H, 9·7. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·8%). All attempts to prepare a dichloro-compound were unsuccessful.

Oxazolidines.—The appropriate anilino-alcohol (5 g.) was rubbed with excess of 40% formaldehyde solution, whereupon (in most cases) a clear solution formed in 1—2 minutes. This then became cloudy

and a heavy colourless oil (or solid) separated, which could be isolated by extraction with ether and purified by distillation or crystallisation; the yields were quantitative. The following were obtained:

Compound.	M. p. or b. p. (solvent).	Found, C, %.	Found, H, %.	Formula.	Required, C, %.	Required, H.
3-*Phenyloxazolidine*	B. p. 94°/1·5 mm., m. p. 28° (pentane)	70·8	7·3	$C_9H_{11}ON$	70·6	7·3
3-p-*Methoxyphenyloxazolidine*	Plates, m. p. 88° (light petroleum)	67·0	7·5	$C_{10}H_{13}O_2N$	67·0	7·5
3-*Phenyl-5-methyloxazolidine* *	B. p. 120°/6 mm., m. p. 37—38° (pentane)	73·2	8·0	$C_{10}H_{13}ON$	73·6	8·0
3-*Phenyl*-1 : 3-*oxazine* *	B. p. 94°/0·4 mm.	73·7	7·8	$C_{10}H_{13}ON$	73·6	8·0
3-*Phenylpentoxazolidine* (3-*phenyl*-1-*oxa*-3-*azacycloheptane*)	B. p. 115°/0·4 mm.	74·6	8·7	$C_{11}H_{15}ON$	74·7	8·7
2 : 3-*Diphenyloxazolidine* †	Needles, m. p. 84—85° (methanol)	80·0	7·1	$C_{15}H_{15}ON$	80·0	6·7

* Purified by chromatography. † Benzaldehyde used in place of formaldehyde.

Diamines.—*NN'-Diphenyl-NN'-di-(2-hydroxyethyl)ethylenediamine.* 2-Anilinoethanol (0·2 mol.), ethylene dibromide (0·1 mol.), chalk (0·15 mol.), and water (100 c.c.) were boiled under reflux with mechanical stirring for 10 hours. The product was extracted with benzene, evaporated, and distilled; the fraction, b. p. 220—230°/0·7 mm., obtained in 74% yield, solidified and crystallised from benzene–light petroleum (b. p. 60—80°) in plates, m. p. 89—90° (Found: C, 72·2; H, 8·0. $C_{18}H_{24}O_2N_2$ requires C, 72·0; H, 8·1%).

NN'-Diphenyl-NN'-di-(2-chloroethyl)ethylenediamine formed stout needles, m. p. 81—82°, from light petroleum (b. p. 40—60°) (Found: C, 64·0; H, 6·3. $C_{18}H_{22}N_2Cl_2$ requires C, 64·1; H, 6·6%).

The following compounds were prepared by exactly similar methods unless otherwise stated:

NN'-Diphenyl-NN'-di-(2-hydroxyethyl)trimethylenediamine, b. p. 210—222°/0·6 mm., flattened needles (from benzene–light petroleum), m. p. 112—113° (75%) (Found: C, 72·8; H, 8·6. $C_{19}H_{24}O_2N_2$ requires C, 72·6; H, 8·3%).

NN'-Diphenyl-NN'-di-(2-chloroethyl)trimethylenediamine, an oil (Found: C, 65·1; H, 7·1. $C_{19}H_{22}N_2Cl_2$ requires C, 64·9; H, 6·9%).

NN'-Diphenyl-NN'-di-(2-hydroxyethyl)tetramethylenediamine. In the preparation of this compound and its pentamethylene analogue no chalk or water was used, the components being heated on the steam-bath for 6 hours, and the cooled mixture then treated with an excess of 2*N*-sodium hydroxide. The fraction, b. p. 200—220°/0·5 mm. (18% yield), solidified and was rubbed with ether, and then crystallised from benzene–light petroleum, forming plates, m. p. 79—80° (Found: C, 73·3; H, 8·5. $C_{20}H_{26}O_2N_2$ requires C, 73·2; H, 8·6%).

NN'-Diphenyl-NN'-di-(2-chloroethyl)tetramethylenediamine crystallised from pentane in prisms, m. p. 65° (Found: C, 65·4; H, 7·0. $C_{20}H_{24}N_2Cl_2$ requires C, 65·7; H, 7·2%).

NN'-Diphenyl-NN'-di-(2-hydroxyethyl)pentamethylenediamine was obtained exactly like the tetramethylene compound (yield 22%); the crude fraction, b. p. 200—210°/0·4 mm., was analysed (Found: C, 72·6; H, 8·6. $C_{21}H_{28}O_2N_2$ requires C, 73·7; H, 8·8%).

NN'-Diphenyl-NN'-di-(2-chloroethyl)pentamethylenediamine was a colourless oil, b. p. 170°/0·2 mm. (Found: C, 66·4; H, 7·6. $C_{21}H_{26}N_2Cl_2$ requires C, 66·5; H, 7·4%).

NN'-Diphenyl-NN'-di-(2-hydroxyethyl)hexamethylenediamine, obtained in 66% yield from *NN'*-diphenylhexamethylenediamine (von Braun, *Ber.*, 1910, **43**, 2859) and ethylene chlorohydrin by the chalk and water process, had b. p. 280°/2 mm. (Found: C, 74·0; H, 9·1. $C_{22}H_{30}O_2N_2$ requires C, 74·1; H, 9·1%).

NN'-Diphenyl-NN'-di-(2-chloroethyl)hexamethylenediamine was crystallised successively from light petroleum (b. p. 40—60°), alcohol, and again light petroleum, forming prisms, m. p. 66° (Found: C, 67·1; H, 8·0. $C_{22}H_{28}N_2Cl_2$ requires C, 67·2; H, 7·7%).

NN'-Diphenyl-NN'-di-(2-hydroxypropyl)ethylenediamine was produced in 61% yield from 2-anilinopropanol and ethylene dibromide. It was also formed on heating *NN'*-diphenylethylenediamine with an excess of propylene oxide in a sealed tube to 160° for 18 hours and was an oil, b. p. ~220°/0·1 mm. (Found: C, 73·2; H, 8·6. $C_{20}H_{26}O_2N_2$ requires C, 73·2; H, 8·6%). In the latter preparation there was formed a by-product boiling some 10° lower and forming plates (from methanol), m. p. 166—167°, probably 2-*ethyl*-1 : 3-*diphenyltetrahydroglyoxaline* (Found: C, 80·5; H, 8·3. $C_{17}H_{18}N_2$ requires C, 80·9; H, 8·0%). The formation of this compound presupposes the rearrangement of propylene oxide to propaldehyde which is known to occur at high temperature (Ipatiew and Leontowitsch, *Ber.*, 1903, **36**, 2017). When the reaction with propylene oxide was interrupted after 10 hours, the product was a solid, prisms (from benzene–light petroleum), m. p. 92°, consisting of *NN'-diphenyl*-N-(2-*hydroxypropyl*)-*ethylenediamine* (Found: C, 75·4; H, 8·0. $C_{17}H_{22}ON_2$ requires C, 75·5; H, 8·2%). The *picrate* had m. p. 142° (Found: N, 14·4. $C_{23}H_{25}O_9N_5$ requires N, 14·0%).

NN'-Diphenyl-NN'-di-(2-chloropropyl)ethylenediamine was an oil (Found: C, 65·5; H, 7·3. $C_{20}H_{24}N_2Cl_2$ requires C, 65·7; H, 7·2%).

NN'-Diphenyl-NN'-di-(3-hydroxypropyl)ethylenediamine (66% yield from 3-anilinopropanol) had m. p. 75° after crystallisation from benzene–light petroleum (b. p. 60—80°) (Found: C, 72·9; H, 8·8. $C_{20}H_{26}O_2N_2$ requires C, 73·2; H, 8·6%).

NN'-Diphenyl-NN'-di-(3-chloropropyl)ethylenediamine formed small prisms, m. p. 53·5—54°, after two crystallisations from pentane (Found: C, 66·1; H, 7·2. $C_{20}H_{24}N_2Cl_2$ requires C, 65·7; H, 7·2%).

NN'-Diphenyl-NN'-di-(4-hydroxybutyl)ethylenediamine (54% yield from 4-anilinobutanol) boiled at 220—240°/0·5 mm. and formed needles, m. p. 81°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 74·1; H, 9·1. $C_{22}H_{30}O_2N_2$ requires C, 74·1; H, 9·1%).

NN'-Diphenyl-NN'-di-(4-chlorobutyl)ethylenediamine formed plates, m. p. 61°, from pentane (Found: C, 67·2; H, 8·1. $C_{22}H_{30}N_2Cl_2$ requires C, 67·2; H, 7·7%).

NN'-Di-(p-methoxyphenyl)-NN'-di-(2-hydroxyethyl)ethylenediamine, obtained in 62% yield from *N*-(2-hydroxyethyl)-*p*-anisidine (Ross, *J.*, 1949, 183), crystallised from benzene–light petroleum (b. p. 60—80°) in fine needles, m. p. 92—93° (Found: C, 66·2; H, 8·2. $C_{20}H_{28}O_4N_2$ requires C, 66·6; H, 7·8%).

NN'-Di-(p-methoxyphenyl)-NN'-di-(2-chloroethyl)ethylenediamine formed lustrous plates, m. p. 63—64° after crystallisation from light petroleum (b. p. 60—80°) (Found: C, 60·6; H, 6·4. $C_{20}H_{26}O_2N_2Cl_2$ requires C, 60·5; H, 6·6%).

NN'-Di-2-naphthyl-NN'-di-(2-hydroxyethyl)ethylenediamine. *NN'*-Di-2-naphthylethylenediamine (Bischoff and Hausdorfer, *Ber.*, 1890, **23**, 1985) (15 g.) was heated in a sealed tube with 5·5 c.c. of ethylene oxide and 5 c.c. of benzene for 12 hours at 160°. The residue obtained after evaporation of the solvent solidified and crystallised from benzene–light petroleum (b. p. 60—80°) in pearly plates, m. p. 96—97° (80%) (Found: C, 78·0; H, 7·1. $C_{26}H_{28}O_2N_2$ requires C, 78·0; H, 7·1%).

NN'-Di-2-naphthyl-NN'-di-(2-chloroethyl)ethylenediamine crystallised from benzene–light petroleum (b. p. 40—60°) in plates, m. p. 124—125° (Found: C, 71·5; H, 6·1. $C_{26}H_{26}N_2Cl_4$ requires C, 71·6; H, 6·0%).

NN'-Di-1-naphthyl-NN'-di-(2-hydroxyethyl)ethylenediamine, obtained in the same way as the 2-naphthyl derivative, formed plates, m. p. 92—93°, from benzene–light petroleum (Found: C, 78·1; H, 7·2. $C_{26}H_{28}O_2N_2$ requires C, 78·0; H, 7·1%). The *dipicrate* had m. p. 125° (Found: C, 53·3; H, 3·9. $C_{38}H_{34}O_{14}N_8$ requires C, 53·1; H, 4·0%).

NN'-Di-1-naphthyl-NN'-di-(2-chloroethyl)ethylenediamine crystallised from light petroleum (b. p. 60—80°) in stout prisms, m. p. 111° (Found: C, 71·6; H, 6·2. $C_{26}H_{26}N_2Cl_4$ requires C, 71·5; H, 6·0%).

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THE CHESTER BEATTY RESEARCH INSTITUTE,
THE ROYAL CANCER HOSPITAL, FULHAM ROAD,
LONDON, S.W.3.

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202. *The Nitration of Polystyrene.*

By H. ZENFTMAN.

Polystyrene has been nitrated with mixtures of nitric and sulphuric acids. By regulating the conditions of nitration, products with degrees of substitution between 1·0 and 2·0 (nitrogen content, 9·4—14·4%) could be obtained, but attempts to obtain higher substitution were unsuccessful. Oxidative fission of nitropolystyrenes produced *p*-nitrobenzoic and 2 : 4-dinitrobenzoic acids. During nitration some degradation of the original polystyrene chain took place, but could be controlled under suitable conditions. The properties of various nitropolystyrenes have been determined.

In the first recorded nitration of polystyrene Blyth and Hofmann (*Annalen*, 1845, **53**, 316) boiled a glassy polymer of styrene with fuming nitric acid and obtained a product of 10·6% nitrogen content which they called "nitrometastyrol." This product was soluble in nitric acid and sulphuric acid, but insoluble in most other solvents. Elementary analysis of this product led these authors to incorrect formulations for styrene and nitrostyrene. Bachman *et al.* (*J. Org. Chem.*, 1947, **12**, 108) nitrated polystyrene with fuming nitric acid in a similar way at 50° and 150° and obtained products with 10·0 and 11·22% of nitrogen, respectively. They were unable to obtain dinitropolystyrene. Recent knowledge of high polymers suggested that a range of nitropolystyrenes differing in chain length and degree of nitration, and consequently in solubility and solution viscosity, should be accessible by suitable choice of starting material and nitration conditions.

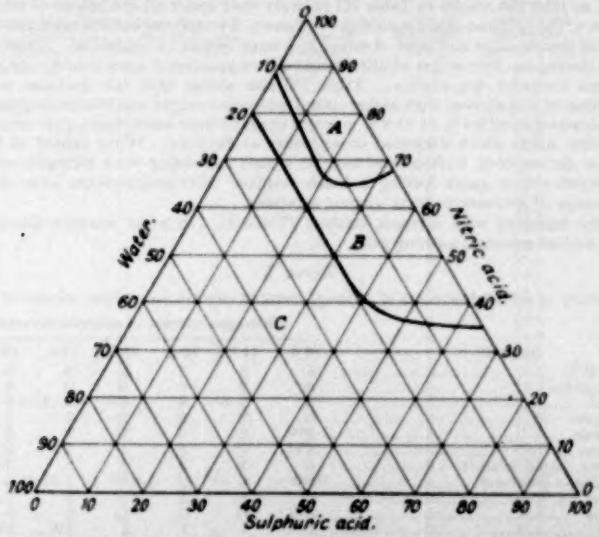
Preliminary experiments showed that nitration of polystyrene in a non-solvent medium merely gave a negligible surface reaction. When the nitrating medium caused swelling of the granules the nitration was more pronounced, but the product was not uniform and unchanged polymer still persisted. It was, therefore, essential to use a nitrating medium capable of completely dissolving the polystyrene. Mixtures of nitric and sulphuric acids were found to be the most suitable nitrating agents for this work. Investigation of the solubility of polystyrene after two hours at 20° in variants of the system nitric acid–sulphuric acid–water gave the results summarised in the triangular diagram.

Area *A* included all nitrating media of practical importance, and the curved boundary of area *C* indicated the approximate minimum degree of dilution required to precipitate the product. Table II summarises the effects of times from 1 to 24 hours and temperatures from 10° to 50° on using various nitrating acids having compositions lying within area *A*.

It was found that polystyrene was nitrated by every nitric or nitric–sulphuric acid

composition capable of dissolving it. The lowest nitrogen content of nitropolystyrene obtained from clear solutions was approximately 9·4%, corresponding to one nitro-group per styrene unit, whereas the highest nitrogen content obtained was 14·4%, corresponding to two nitro-groups per styrene unit. Any intermediate substitution could be obtained by controlling the composition of the nitrating acid, the temperature, and the time of nitration. The molecular weight of the initial polystyrene (as indicated by the viscosity data in Table IV) was found to have little influence on the nitrogen content of the final product. The introduction of the first nitro-group was rapid and appeared to accompany the dissolution of the polystyrene. The rate of mononitration could be regulated by modifying the rate of dissolution of polystyrene in the nitrating acid, *e.g.*, by variation of the particle size. Introduction of the second group took place at a slower rate which was dependent on the dilution of the nitrating acid and the temperature of nitration. Addition of polystyrene to nitrating acid was always accompanied by evolution of heat, and efficient stirring and cooling were necessary to control the nitration. It was observed, however, during renitration of nitropolystyrene (9·8% nitrogen content) to a higher nitrogen content (14·1%) that it dissolved in the nitric–sulphuric acid quickly but without significant evolution of heat. For each nitrating acid composition and temperature of nitration there was a limiting degree of substitution which, as a rule, was attained more rapidly the higher the temperature. Attempts were made to obtain nitropolystyrene of a higher degree of substitution than 2·0 by carrying out nitration in sealed tubes at high temperatures (120° and 150°), but these met with no success. The nitrogen contents of the products were determined by the Dumas method. Elementary analyses of a few samples of nitropolystyrene of various nitrogen contents were consistent with the expected empirical formula $C_8H_{8-n}(NO_2)_n$, where n represents the degree of substitution calculated from the equation $n = 104N/(1400 - 45N)$ (where N = % of nitrogen).

Solubility of polystyrene in nitric acid–sulphuric acid–water mixtures.



Area A. Solubility. Area B. Gelatinisation. Area C. Insolubility.

The positions of the nitro-groups in the polymeric chain were determined by oxidative fission of nitropolystyrenes. Aromatic nitro-compounds with an aliphatic side chain are readily oxidised to the corresponding nitrobenzoic acids. Bigelow (*J. Amer. Chem. Soc.*, 1919, **41**, 1578) obtained good yields of mononitrobenzoic acids from mononitrotoluenes by using potassium permanganate in alkaline solutions. For the same purpose Feldman *et al.* (*J. Gen. Chem. Russia*, 1945, **15**, 962) used manganese dioxide and concentrated sulphuric acid. Dinitro-

toluenes were oxidised to dinitrobenzoic acids by Sirks (*Rec. Trav. chim.*, 1908, **27**, 221), using nitric acid or potassium permanganate, and by Buehler and Calfee (*Anal. Chem.*, 1934, **6**, 351), using chromic acid.

Oxidation of nitropolystyrenes to nitrobenzoic acids was found to be difficult, and all methods gave large amounts of unchanged nitropolystyrene. The best results were obtained by using manganese dioxide in concentrated sulphuric acid. Only *p*-nitrobenzoic and 2 : 4-dinitrobenzoic acids could be isolated. Nitropolystyrene of a nitrogen content 9·4% (degree of substitution 1·0) gave on oxidation only *p*-nitrobenzoic acid, but nitropolystyrenes with a degree of substitution between 1 and 2 always gave both *p*-nitrobenzoic and 2 : 4-dinitrobenzoic acids. All attempts to isolate mononitrobenzoic acids from the oxidation of a nitropolystyrene of a degree of substitution approximately 2·0 were unsuccessful, and this suggested the absence of nitro-groups in the aliphatic chain.

These results indicated that during nitration of polystyrene only nuclear substitution occurred, a maximum of two nitro-groups entering each benzene ring. The first group entered the *p*-position, the second being randomly distributed along the polymer chain entirely or predominantly in the *o*-position. It was not possible, however, to state definitely that substitution was entirely limited to the *o*- and the *p*-positions on account of the low yields of nitrobenzoic acids calculated on unrecovered nitropolystyrene (usually less than 40%).

Degradation of the chain length of the polystyrene during nitration was estimated approximately by measuring the viscosities of the nitrated products and the original polystyrene. Viscosities were measured in dilute *cyclo*hexanone solutions at such concentration that $\eta_{rel.}$ had values between 1·1 and 1·2, and were applied to the following approximation of Staudinger's expression: Degree of polymerisation $= k(\eta_{rel.} - 1)/C$; k for nitropolystyrene was unknown, but may be taken as constant in the range of nitrogen contents under consideration.

It is, moreover, considered unlikely that k for polystyrene will be halved when the material is nitrated, so that the results in Table III indicate that under all conditions of nitration some degradation of the polymer chain occurred. However, by carrying out the nitration under strict conditions of temperature and time, it could to a large extent be controlled. Degradation was most rapid during the first stages of nitration and then continued more slowly. High nitration temperatures favoured degradation. Table IV also shows that the decrease in degree of polymerisation of polystyrene with higher initial molecular weight was relatively greater.

Nitropolystyrenes of 9·4% to 14·4% nitrogen content were amorphous, pale cream-coloured to light yellow solids which darkened on exposure to daylight. When heated to 300°, nitropolystyrenes decomposed without melting, at a rate increasing with nitrogen content, and evolved greyish-yellow gases leaving a black residue. Nitropolystyrenes were soluble in a restricted range of solvents to form viscous solutions.

Solubility increased with nitrogen content (Table I). In some solvents nitropolystyrene underwent limited swelling, forming gels.

TABLE I.

Solubility of nitropolystyrenes of different nitrogen contents in various solvents at 20°.

Solvent.	Nitrogen content of nitropolystyrene, %.						
	9·8.	11·7.	12·4.	13·0.	13·4.	13·8.	14·4.
Nitric acid, 90%	S	S	S	S	S	S	S
Ethylene dinitrate	S	S	S	S	S	S	S
Nitroglycerol	S	S	S	S	S	S	S
Furfuraldehyde	G	S	S	S	S	S	S
*cyclo*Pentanone	SW	S	S	S	S	S	S
*cyclo*Hexanone	SW	G	*S*	*S*	*S*	*S*	*S*
Dinitrotoluene (liquid mixture)	*G*	*S*	*S*	*S*	*S*	*S*	*S*
Mononitrotoluene (mixture)	SW	*G*	*G*	*S*	*S*	*S*	*S*
Nitrobenzene	G	*S*	*S*	*S*	*S*	*S*	*S*
Nitromethane	SW	G	G	G	G	G	G
Acetone	I	I	I	I	SW	SW	SW

S = soluble at 20°. *S* = requires heating to facilitate dissolution, remains in solution when cooled to 20°. G = gelatinised. *G* = gelatinised when heated. SW = swelling observed. I = no visible reaction.

EXPERIMENTAL.

Nitration of Polystyrene.—Nitration was carried out by adding granular polystyrene to a 10—20-fold weight of nitrating acid with vigorous stirring. The initial temperature of the acid was about −10°, and the whole of the polystyrene was added within 2—3 minutes. The temperature increased immediately after addition of polystyrene but effective cooling prevented it from exceeding 20°. After approximately

30 minutes the temperature was kept steady at the desired point, and maintained there by either cooling or heating. The viscosity of the mixture increased and the rate of stirring was reduced. Rapid addition of polystyrene to acid at low temperature was a necessary condition for obtaining a product with consistent properties. If the addition was carried out slowly at a constant temperature the rise of viscosity hindered the immersion and dispersion of further portions of polystyrene and caused local overheating of the particles. This was indicated by the appearance of brown fumes, and also by an excessively degraded product. When the nitration was finished, the mixture formed a clear, straw-coloured or brown, viscous liquid. Nitropolystyrene was precipitated from the solution by running the liquid in one or many very thin streams into gently stirred cold water. The precipitated product formed coils of threads which gradually became brittle and finally broke up into easily handled elongated granules which were sufficiently porous to permit washing out of the last traces of acid. When mechanical losses were avoided the weight of product as a percentage of the weight of initial polystyrene, approximated to the theoretical value of $100 + 100N/(31{\cdot}11 - N)$ % (N = % of nitrogen).

A typical nitration was carried out as follows: Mixed acid (300 ml.; composition: HNO_3, 73·2; H_2SO_4, 26·3; HNO_2, 0·1; H_2O, 0·4%) was cooled to −10° in a wide-necked conical flask. Polystyrene (125 g.; M, 210,000; particle size, 16—30 B.S. gauge) was added during two minutes, the temperature rising to 18°. Cooling with ice-salt and effective stirring during the first 30 minutes were required to prevent a further rise of temperature. After 30 minutes the temperature settled at 20°. After 1 hour from the start the whole of polystyrene had dissolved. Slow stirring was maintained for a further 3 hours at 20°, and the solution was then run from a dropping-funnel during 40 minutes into slowly stirred water (4—5 l.). The thread-like product was broken up into short lengths, washed five times by decantation, filtered off, washed on the filter, and steeped in water overnight. The filtered product was ground for 16 hours in a porcelain ball-mill with water (approx. 5 parts). Filtration, washing with water at 90—95° until the washings were neutral to methyl-orange, and drying to constant weight gave a product (42 g.) containing N, 13·4% (by Dumas's method). The degree of substitution was found to be 1·75, and ultimate analysis gave C, 51·9; H, 3·1% [Calc. for $C_8H_{8\cdot25}(NO_2)_{1\cdot75}$: C, 52·5; H, 3·4%].

TABLE II.

Influence of conditions of nitration on nitrogen content of nitropolystyrene.

Nitrating acid composition, %.				Temp. of nitration.	Time of nitration (hrs.).	Nitrogen content of nitropolystyrene (%).	Degree of substitution (s).
HNO_3.	H_2SO_4.	HNO_2.	H_2O.				
72·73	28·09	0·24	−1·06	10°	1	12·4	1·53
,,	,,	,,	,,	,,	2	12·8	1·62
,,	,,	,,	,,	,,	3	13·2	1·70
,,	,,	,,	,,	,,	5	13·3	1·73
,,	,,	,,	,,	,,	7	13·4	1·75
,,	,,	,,	,,	,,	24	13·4	1·75
,,	,,	,,	,,	20	1	12·8	1·62
,,	,,	,,	,,	,,	2	13·3	1·73
,,	,,	,,	,,	,,	3	13·4	1·75
,,	,,	,,	,,	,,	4	13·4	1·75
,,	,,	,,	,,	,,	5	13·6	1·80
,,	,,	,,	,,	30	1	13·1	1·68
,,	,,	,,	,,	,,	3	13·7	1·82
,,	,,	,,	,,	,,	4	14·1	1·92
,,	,,	,,	,,	,,	6	14·1	1·92
,,	,,	,,	,,	40	1	13·3	1·73
,,	,,	,,	,,	,,	2	13·8	1·84
,,	,,	,,	,,	,,	4	14·3	1·97
,,	,,	,,	,,	50	1	13·7	1·82
,,	,,	,,	,,	,,	2	14·2	1·94
,,	,,	,,	,,	,,	3	14·4	2·00
72·98	22·29	0·25	4·48	20	1	11·7	1·39
,,	,,	,,	,,	,,	3	12·0	1·45
,,	,,	,,	,,	,,	4	12·8	1·62
,,	,,	,,	,,	,,	5	13·1	1·68
,,	,,	,,	,,	,,	6	13·3	1·73
76·75	15·30	0·10	7·85	20	1	10·0	1·09
,,	,,	,,	,,	,,	3	11·6	1·37
,,	,,	,,	,,	,,	4	11·8	1·41
,,	,,	,,	,,	,,	6	12·1	1·47
66·40	20·30	0·10	13·20	20	2	9·5	1·02
,,	,,	,,	,,	,,	4	9·7	1·05
,,	,,	,,	,,	,,	6	9·8	1·06

Molecular weight of polystyrene used, 210,000. Ratio of acid to polystyrene, 20 : 1.

Oxidation of High-nitrogen Nitropolystyrene with Manganese Dioxide.—Finely ground nitropolystyrene (50 g.; N, 14·2%) was suspended in 96% (w/w) sulphuric acid (250 ml.) and left overnight. The liquid was heated in an oil-bath to 135°, and manganese dioxide (170 g.; MnO_2 content, 80%) was added during 16 hours in small portions at intervals of 15—20 minutes. The hot liquid was poured on crushed ice

(900 g.), and the product filtered, giving a solid residue (i) and a filtrate (ii). Residue (i) was washed with water (150 ml.), the washings being added to (ii), then suspended in water (200 ml.), made alkaline with concentrated sodium carbonate solution, heated to 85°, and filtered hot, giving a filtrate (iii) and a residue (iv). Residue (iv) was washed with hot water, separated by decantation from heavy particles of manganese dioxide, heated with diluted sulphuric acid, filtered, washed, and dried to constant weight to yield unconverted nitropolystyrene (30 g.). Filtrate (iii) was made acid (Congo-red paper) with the minimum amount of sulphuric acid (70% w/w), cooled, and filtered from traces of precipitate, giving filtrate (v).

TABLE III.

Influence of temperature and time of nitration on the viscosity of nitropolystyrene.

Nitration conditions.		Product.			
Temp.	Time (hrs.).	Nitrogen content (%).	C, g./100 ml.	$\eta_{rel.}$	$(\eta_{rel.}-1)/C$.
20°	2	13·2	0·165	1·148	0·90
,,	4	13·4	0·217	1·165	0·76
,,	5	13·6	0·209	1·142	0·71
30	1	13·1	0·220	1·151	0·69
,,	3	13·7	0·209	1·118	0·59
,,	4	14·1	0·204	1·107	0·52
40	1	13·3	0·200	1·106	0·53
,,	2	13·8	0·212	1·106	0·50
,,	4	14·3	0·224	1·108	0·48
50	1	13·7	0·306	1·119	0·39
,,	2	14·2	0·286	1·103	0·36
,,	3	14·4	0·323	1·120	0·34

The original polystyrene used in these nitrations had $(\eta_{rel.}-1)/C = 1·87$ (determined in *cyclo*hexanone, $C = 0·060$). Nitrating acid used: HNO_3, 72·7; H_2SO_4, 28·1; HNO_3, 0·2; H_2O, −1·0%.

TABLE IV.

Influence of viscosity of the polystyrene on the nitrogen content and the viscosity of nitropolystyrene.

Polystyrene.	Nitropolystyrene.		Polystyrene.	Nitropolystyrene.		Polystyrene.	Nitropolystyrene.	
$(\eta_{rel.}-1)/C$.	N, %.	$(\eta_{rel.}-1)/C$.	$(\eta_{rel.}-1)/C$.	N, %.	$(\eta_{rel.}-1)/C$.	$(\eta_{rel.}-1)/C$.	N, %.	$(\eta_{rel.}-1)/C$.
1·05	13·58 13·52	0·54	1·87	13·48 13·41	0·76	4·80	13·45 13·42	1·07

Composition of nitrating acid: HNO_3, 72·2; H_2SO_4, 26·4; HNO_3, 0·2; H_2O, 1·2%. Temperature, 20°; time, 4 hours.

Filtrate (v) gave a residue (vi; 1·1 g.) on extraction with ether (100 ml.) and evaporation of the extract. Residue (vi) was dissolved in the minimum amount of hot water, and decolorised with charcoal. Successive crops of crystals had m. p.s between 178° and 182°, which were not depressed on admixture with 2 : 4-dinitrobenzoic acid.

Filtrate (ii) was extracted with ether (150 ml.), 300 ml. of (ii) being used at a time, and the ether extract re-used. After evaporation, residue (vii) was obtained (7·7 g.). Residue (vii), crystallised from water (charcoal), gave crops of crystals with m. p.s between 177° and 181°, undepressed on admixture with 2 : 4-dinitrobenzoic acid.

Oxidation of Low-nitrogen Nitropolystyrene with Manganese Dioxide.—Nitropolystyrene (20 g.; N, 12·3%) was suspended in 75% (w/w) sulphuric acid (300 g.), and manganese dioxide (95 g.; MnO_2 content, 80%) was gradually added at 135° during 12 hours. The liquid was poured into water (350 ml.) and filtered when cold, giving a residue (i) and a filtrate (ii). Residue (i) was washed with water (50 ml.), the washings being added to (ii), and the residue suspended in water (120 ml.), made alkaline, and filtered hot, giving a filtrate (iii) and residue (iv). Residue (iv), washed with dilute sulphuric acid and water, dried, and analysed for nitrogen, was shown to contain nitropolystyrene (11·5 g.).

Ether-extraction of filtrate (ii) yielded 2 : 4-dinitrobenzoic acid (1·3 g.). Filtrate (iii) was made acid, left overnight in a cool place, and filtered to give a residue (v) and filtrate (vi). Residue (v) and the ethereal extract of filtrate (vi) gave crystals (total yield 1·5 g.) which on recrystallisation from water had m. p. 241° (undepressed by *p*-nitrobenzoic acid).

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IMPERIAL CHEMICAL INDUSTRIES LIMITED,
NOBEL DIVISION, STEVENSTON, AYRSHIRE.

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203. *The Electrical Conductivity of Iodine Monochloride and Iodine Trichloride.*

By N. N. Greenwood and H. J. Emeléus.

The electrical conductivity of molten iodine monochloride passes through a maximum at 40°. The conductivity of solid and liquid iodine trichloride has been measured in the range 70—150°. That of the solid increased rapidly with increasing temperature. There was no marked discontinuity at the melting point. In the molten state there was a maximum in the conductivity–temperature curve at 111°. It was shown that the maximum in the case of the monochloride was probably due to a decrease with rising temperature in the number of ions present. The degree of ionisation in molten iodine monochloride was of the order of 1%. For neither compound was there any indication of a decomposition potential. On prolonged electrolysis of molten iodine monochloride a small back e.m.f. was observed.

Both iodine monochloride and iodine trichloride dissolve in a variety of solvents and in many cases such solutions are found to conduct electricity. For instance, iodine monochloride is a conductor when dissolved in acetic acid, nitrobenzene, arsenic trichloride, sulphur dioxide, sulphuryl chloride, or water, and the trichloride conducts in all of these solvents, as well as in dichloroacetic acid and liquid bromine. Solutions of iodine trichloride in carbon tetrachloride, silicon tetrachloride, and chloroform are, however, non-conducting (Plotnikov and Rokotyan, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 723). Evidence for the nature of the ions in the molten iodine chlorides cannot readily be obtained directly but in the above solutions fairly definite deductions may be made. In the case of solutions of iodine monochloride dissociation into I^+ and $[ICl_2]^-$ appears most likely. This explains why electrolysis results in the deposition of iodine at both the cathode and the anode since, at the latter, a disproportionation of ICl_2 into I and ICl_3 (or I and Cl) could occur. This also explains why the concentration of both halogens (either free or in combined form) increases at the anode although the ratio of iodine to chlorine decreases (Sandonnini and Borgello, *Atti Accad. Lincei*, 1937, **25**, 46).

The nature of the ions formed by iodine trichloride in solution is less clear. Bruns (*Z. physikal. Chem.*, 1925, **118**, 89) claimed that, when an acetic acid solution was electrolysed, the whole of the iodine trichloride migrated to the anode. To explain this and also certain dilution effects the equilibrium $ICl_3,nCH_3{\cdot}CO_2H \rightleftharpoons ICl_3^{---} + (CH_3{\cdot}CO_2H)_n^{++}$ was postulated. Other equilbria which have been suggested are: $ICl_3 \rightleftharpoons I^{+++} + 3Cl^-$ and $ICl_3 \rightleftharpoons I^+ + Cl_3^-$. Yet another possibility, which is supported by the existence of salts such as $KICl_4$, is: $2ICl_3 \rightleftharpoons ICl_2^+ + ICl_4^-$. It is not certain that the ions in the molten compound will be identical with those in solution, but for the purposes of calculations of ion concentrations made later, the existence of I^+ and ICl_2^- in molten ICl has been assumed. The conductivity of molten iodine monochloride at 35° was measured by Cornog and Karges (*J. Amer. Chem. Soc.*, 1932, **54**, 1882), who showed that after repeated crystallisation the specific conductivity at this temperature was $4{\cdot}57$—$4{\cdot}59 \times 10^{-6}$ohm^{-1}cm.$^{-1}$. The compound was also shown to behave as an ionising solvent towards potassium chloride and ammonium chloride. Fialkov and Goldman (*J. Gen. Chem. Russia*, 1941, **11**, 910) found a conductivity of $4{\cdot}87$—$5{\cdot}39 \times 10^{-6}$ohm^{-1}cm.$^{-1}$ at 35° after purification by distillation at atmospheric pressure. During the course of the work described below, Fialkov and Shor (*Zhur. Obsch.*, 1948, **18**, 14) showed the existence of an extended maximum in the temperature–conductivity curve for molten iodine monochloride. The existence of this maximum was observed independently in the present work, though the absolute values of the conductivity of iodine monochloride were rather lower than those reported by Fialkov and Shor. No previous observations have been recorded on the conductivity of molten iodine trichloride, which also passes through a maximum. A discussion of these maxima and of the absence of a decomposition potential in either of the iodine chlorides is given later.

Experimental.

Iodine monochloride, prepared by Cornog and Karges's method (*loc. cit.*), was purified by recrystallisation in a static vacuum in an apparatus, shown in Fig. 1, in which a conductivity cell of the conventional type with sealed-in platinum electrodes was incorporated. About 100 g. of the monochloride were melted in the right-hand bulb, about 80% of the melt was allowed to crystallise, and the supernatant liquid was poured into the left-hand bulb. This process was repeated until the final batch of crystals showed the same m. p. on two successive operations. Usually four or five recrystallisations were found to give extremely pure iodine chloride having m. p. 27·20° as given by Cornog and Karges (*loc. cit.*). These pure crystals were then melted and poured into the cell, which was sealed at the constriction. Conductivities were measured by using the amplified output of a 1000-cycle oscillator in a Wheatstone-type network, and the balance point was detected electronically with a cathode-ray oscilloscope. The thermostat was controlled to $\pm 0{\cdot}03°$ by a contact thermometer in a large oil-bath.

The results obtained are shown in Fig. 2. Curve I shows data for impure iodine monochloride between the m. p. (27·2°) and 65°. Curve II represents the results for a purer sample: not only is the conductivity less, but there is a maximum at 45°. In Curve III and Table I the results for highly purified iodine monochloride are summarised. The conductivity is still lower and the maximum has been displaced to 40°. The data in Table I were reproducible, the value of $4{\cdot}60 \times 10^{-6}$ ohm^{-1}cm.$^{-1}$ for the conductivity at 35° being in close agreement with Cornog and Karges's value (*loc. cit.*). In col. 4 the values of a quantity μ/n are given. This function has been extensively used to compare the conductivities of molten chlorides at their melting points (Biltz and Klemm, *Z. anorg. Chem.*, 1926,

Fig. 1.

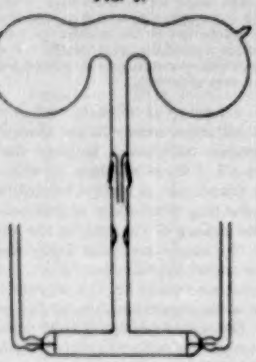
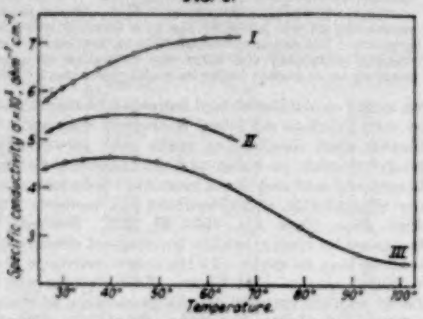


Fig. 2.



Iodine monochloride: I, impure; II, partly purified; III, highly purified.

152, 267). The quantity n is defined to be one less than the number of ions formed by dissociation of one molecule, and has been taken as unity for iodine monochloride.

Table I.

Conductivity of molten iodine monochloride between 27° and 120°.

Temp.	$\sigma \times 10^3$ (ohm^{-1} cm.$^{-1}$).	Density (d) (g./cm.^{3}).*	$\mu/n = M\sigma/dn$.	Temp.	$\sigma \times 10^3$ (ohm^{-1} cm.$^{-1}$).	Density (d) (g./cm.^{3}).*	$\mu/n = M\sigma/dn$.
26·75°	4·403	3·193	0·2217	64·5°	4·057	3·066	0·2149
30·6	4·519	3·180	0·2309	69·0	3·810	3·052	0·2027
34·45	4·593	3·168	0·2355	79·3	3·271	3·017	0·1760
39·9	4·637	3·149	0·2392	81·8	3·068	3·010	0·1655
45·1	4·610	3·131	0·2392	91·4	2·667	2·977	0·1455
49·7	4·541	3·117	0·2366	101·0	2·471	—	—
55·1	4·415	3·098	0·2314	113·0	2·043	—	—
59·8	4·270	3·082	0·2250	122·0	1·817	—	—

* By interpolation from Hannay's data (*J.*, 1873, **26**, 815).

The current–voltage curves obtained in a series of direct-current measurements with iodine monochloride are shown in Fig. 3. Two temperatures were chosen, one above and one below the temperature of maximum conductivity, and in neither case was there any evidence of a decomposition potential. The measurements were extended down to potentials of 1 mv. with the same result. In a parallel experiment, iodine monochloride was electrolysed at 35° in a cell with separate anode and cathode compartments. After a given time the circuit was broken, and the back e.m.f. followed potentiometrically until a steady value had been attained. This having been read, the electrolysis was continued for a further period and the same procedure repeated. Usually, the steady value was attained within 5 minutes of breaking the circuit and was about two thirds of the original value. This back e.m.f. remained constant for one hour. The results are given in Table II. The A.C. resistance of the cell was 24300 ohms, the D.C. voltage 113 v., and the D.C. current 4·65 milliamp. The volume of each electrode compartment was approx. 5 ml. Not only was the back e.m.f. extremely small, but it was also dependent on the amount of electrolysis. An explanation of these effects is presented in the discussion.

Table II.

Time of electrolysis (min.)	30	55	178
Faradays passed, $\times 10^4$	0·868	1·59	5·15
Back e.m.f. (mv.)	7	8·5	11

Iodine Trichlorides.—Pure iodine trichloride was prepared by adding finely powdered resublimed iodine to an excess of liquid chlorine at −78°. The chlorine had been purified by distillation. The excess of chlorine was allowed to evaporate through a silica drying tower. This material was filled

directly into the conductivity cell, which was sealed at atmospheric pressure. The cell was made of Pyrex glass with a 3-mm. wall thickness in order to withstand the high pressure of the molten trichloride at and above its m. p. (101°). This pressure is 16 atm. at 101°. The molten trichloride attacked platinum rapidly but tungsten was not corroded even on prolonged heating. Tungsten rods of 5-mm. diameter were used as electrodes and were ground to 2-mm. diameter where they passed through the glass wall of the cell. The electrical circuit and the thermostatic control were the same as in the experiments on iodine monochloride.

TABLE III.

Conductivity of solid and of liquid iodine trichloride between 70° and 150°.

Temp.	70·0°	79·9°	84·8°	89·9°	95·0°	96·2°	97·7°	99·4°	100·1°	102·0°	103·7°
$\sigma \times 10^3$, ohm^{-1} cm.$^{-1}$	0·0120	0·0597	0·175	0·490	2·64	4·68	6·87	8·25	8·25	8·60	9·13
Temp.	105·3°	107·0°	109·3°	112·5°	115·0°	122·9°	127·0°	131·0°	135·5°	139·0°	142·7°	146·5°
$\sigma \times 10^3$, ohm^{-1} cm.$^{-1}$	9·31	9·40	9·55	9·53	9·34	8·15	6·73	4·52	2·39	1·29	0·69	0·36

The data in Table III show the results of a typical series of measurements made below and above the m. p. of the trichloride on material previously melted and allowed to solidify. These data show

FIG. 3.

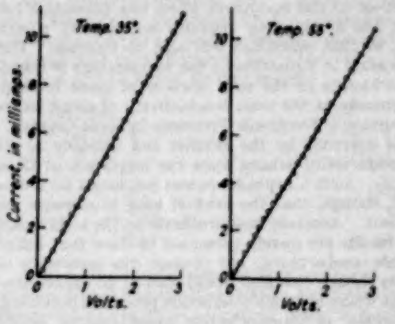
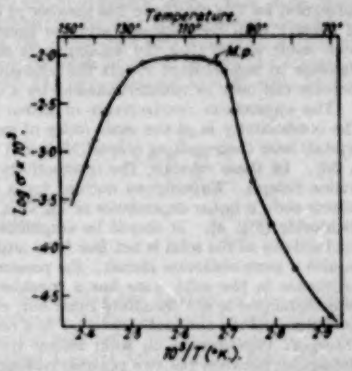


FIG. 4.



that the conductivity of solid iodine trichloride increases rapidly as the temperature is raised and that there is no pronounced discontinuity at the m. p. Above the m. p. the conductivity rises more slowly, passing through a maximum at 111°. Thereafter the value falls and at 145° is equal to that for the solid 10° below the m. p. The existence of the maximum is conveniently represented by plotting the logarithm of the conductivity against the reciprocal of the absolute temperature, as in Fig. 4. As in the case of iodine monochloride, direct-current measurements gave linear current–voltage plots without any indication of the existence of a decomposition potential.

DISCUSSION.

The degree of ionisation required to account for the observed conductivity of iodine monochloride may be calculated very approximately, but the necessary data are not available for the trichloride. By extrapolation of Beck's results (*Z. physikal. Chem.*, 1904, **48**, 641) the viscosity (η) of iodine monochloride at 35° is 3·74 centipoises. From the data of Cornog and Karges (*loc. cit.*) the equivalent conductivity at infinite dilution (λ_∞) of potassium chloride in iodine monochloride is 31·7, from which the product $[\eta . \lambda_\infty]_{\text{KCl in ICl}}$ is 118. The corresponding figure, $[\eta . \lambda_\infty]_{\text{KCl in H}_2\text{O}}$, for an aqueous solution of potassium chloride, is 136. It would therefore seem that Walden's rule applies approximately, the conductivity of potassium chloride varying inversely as the solvent viscosity. The applicability of Walden's rule may be fortuitous, but experimentally it does hold for the conductivity of potassium chloride in iodine monochloride and in water, and this fact may be used to estimate the ionic mobilities by the following argument.

Fialkov and Kaganskaya (*J. Gen. Chem. Russia*, 1948, **18**, 289) have shown that the ionic species present in a solution of potassium chloride in iodine monochloride are K^+ and $[ICl_2]^-$ and that the transference number of the $[ICl_2]^-$ ion is 0·504, a value which is very close to that for the Cl^- ion in an aqueous solution of potassium chloride. It is therefore possible to estimate the mobility of $[ICl_2]^-$ from the known mobility of Cl^- in aqueous

solution ($7{\cdot}9 \times 10^{-4}$ cm./sec. per volt/cm.), as $v_{ICl_2^-} = 7{\cdot}9 \times 10^{-4} \times (\eta_{ICl_2^-}/\eta_{ICl}) \simeq 2 \times 10^{-4}$ cm.^{2}volt^{-1}sec.$^{-1}$. It being assumed to a first approximation that the mobilities of I^+ and ICl_2^- are equal, the average ionic mobility (v) of iodine monochloride may be taken as 2×10^{-4}cm.^{2}volt^{-1}sec.$^{-1}$, a value which is likely to be correct to within a factor of 2. If m is the number of current carriers per c.c. and e is the electronic charge, then as the conductivity at 35° ($\sigma_{35} = mev$) has a value of $4{\cdot}6 \times 10^{-9}$ohm^{-1}cm.$^{-1}$, a value for m of $1{\cdot}4 \times 10^{20}$ carriers/c.c. is obtained. If the value of the density at 35° is taken as 3·165 g.cm.$^{-3}$, 1 c.c. of iodine monochloride contains $1{\cdot}17 \times 10^{22}$ molecules, and the degree of ionisation is therefore $1{\cdot}2 \times 10^{-4}$. Thus, from this approximate calculation, about one in eighty molecules of iodine monochloride is dissociated into ions at 35°, a value which should be correct, at least as far as order of magnitude is concerned.

The specific conductivity data for iodine monochloride show a maximum at 40°. This maximum might arise from opposing density and viscosity effects. The maximum persists, however, when the quantity $\mu/\eta(= M\sigma/d\eta)$ is plotted against temperature. This is shown by the data in the last column of Table I. The quantity μ/η has been used by Biltz and Klemm (*loc. cit.*) to compare the conductivity of molten chlorides at their melting points. It effects a correction for the change in the number of conducting species per c.c. arising from the change of density with temperature, and the persistence of the maximum when this correction has been made shows that the maximum is not due to opposing viscosity and density effects. Increase in temperature lowers the viscosity, so that mobilities will tend to increase. This increase can only be counterbalanced by a decrease in ionisation as the temperature is raised.

The appreciable conductivity of iodine trichloride in the solid state is of great interest. The conductivity is of the same order of magnitude as the ionic conductivity of alkali halide crystals near their melting points (Mott and Gurney, "Electronic Processes in Ionic Crystals," p. 36). In these crystals, the conductivity is governed by the number and mobility of the lattice defects. Expressions derived for a conductivity arising from the migration of these defects show a linear dependence of log σ on $1/T$. Such a dependence was not found for iodine trichloride (Fig. 4). It should be emphasised, though, that the method used to measure the conductivity of the solid is not free from criticism. Accurate measurements on the solid would require a more elaborate circuit; the present results are merely presented to show that iodine trichloride in the solid state has a considerable conductivity. At present, the possibility of semiconduction is not definitely ruled out, even though this also would lead to an exponential dependence of the conductivity on $1/T$ in a range where only one conduction process is occurring. Transport experiments on solid iodine trichloride, or thermoelectric measurements, would distinguish between the two possible conduction mechanisms.

An explanation of the extremely small back e.m.f. generated on electrolysing molten iodine monochloride may be based on the hypothesis that the electrode products are already present in the melt, in thermodynamic equilibrium with iodine monochloride. In this case electrolysis would merely alter the concentration of the products at each electrode and a concentration e.m.f. would be set up on electrolysis. The magnitude of this should depend on the amount of electrolysis, and this effect has been observed (Table II).

If one assumes the electrode products are iodine at the cathode, and iodine trichloride at the anode, then, using the published values of free energy for the reactions concerned, it is possible to show that such a hypothesis does, in fact, reproduce the essential features of the back e.m.f. measurements. In addition, the hypothesis would explain why no decomposition potential is observed when D.C. current–voltage measurements are made. As electrolysis merely alters locally the normal equilibrium concentrations of iodine and iodine trichloride in the melt, and since the amount of electrolysis in the current–voltage measurements is considerably less than that used in the back e.m.f. measurements (see Table II), the back potentials developed would be so small as to be undetectable with the precision of measurement used. It is likely that a similar explanation would account for the absence of a decomposition potential in iodine trichloride and bromine trifluoride, though in these cases the nature of the electrode processes is less certain and the requisite thermodynamic data are not available.

The authors are indebted to Professor R. E. Connick for his assistance in the interpretation of the experimental results. One of the authors (N. N. G.) wishes to thank the Commissioners of the Exhibition of 1851 for the award of an Overseas Studentship, during the tenure of which this work was done.

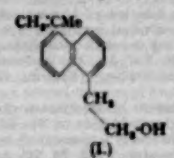
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 14th, 1949.*]

204. *Syntheses in the Phenanthrene Series. Part XI.** 1-*Methyl*-8-*isopropylphenanthrene.*

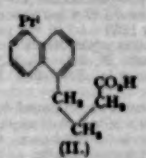
By W. F. Short and H. Wang.

1-Methyl-8-*iso*propylphenanthrene has been synthesised from 1-naphthoic acid via 5-bromo-1-naphthoic acid, γ-5-*iso*propyl-1-naphthylbutyric acid, and 1-keto-8-*iso*propyl-1 : 2 : 3 : 4-tetrahydrophenanthrene. It is identical with the hydrocarbon obtained by the dehydrogenation of totarane.

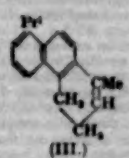
In attempting the synthesis of 1-*methyl*-8-*isopropylphenanthrene* we first prepared 1-*bromo*-8-*isopropenylnaphthalene* by the action of acetone on 5-bromo-2-naphthylmagnesium bromide (Fieser and Riegel, *J. Amer. Chem. Soc.*, 1937, **59**, 2564) but were unable to obtain an addition product from the unsaturated compound and maleic anhydride. We therefore condensed 1-nitronaphthalene with paraformaldehyde and hydrogen chloride (I.G. Farbenindustrie, B.P. 473,522) and converted the resulting 5-nitro-1-chloromethylnaphthalene into 5-*nitro*-1-*hydroxymethylnaphthalene*, 5-nitro-1-naphthaldehyde (Ruggli and Burckhardt, *Helv. Chim. Acta*, 1940, **23**, 445), 5-nitro-1-naphthoic acid (Ruggli and Burckhardt, *loc. cit.*), and 5-*amino*-1-*naphthoic acid*. Satisfactory conditions for the conversion of the amino-acid into 5-bromo-1-naphthoic acid could not be found, and the bromo-compound was therefore prepared by direct bromination of 1-naphthoic acid (Kerkhof, *Rec. Trav. chim.*, 1932, **51**, 747), obtained in 87% yield by the oxidation of 1-naphthyl methyl ketone.



(I.)



(II.)



(III.)

1-*Bromo*-5-*isopropenylnaphthalene*, prepared by dehydrating the product of the reaction between *methyl* 5-*bromo*-1-*naphthoate* and methylmagnesium iodide, could not be reduced to the corresponding *iso*propyl compound owing to preferential removal of the bromine atom. 5-*iso*Propenyl-1-naphthylmagnesium bromide was therefore brought into reaction with ethylene oxide and the resulting 2-5′-*isopropenyl*-1′-*naphthylethyl alcohol* (I) was reduced to 2-5′-*isopropyl*-1′-*naphthylethyl alcohol*. The corresponding *bromide* and ethyl sodiomalonate afforded *ethyl* 2-5′-*isopropyl*-1′-*naphthylethylmalonate* (89%), which was successively hydrolysed to the acid, m. p. 151—152°, and decarboxylated to γ-5-*isopropyl*-1-*naphthylbutyric acid* (II), m. p. 120—121°. The acid was dehydrated to 1-*keto*-8-*isopropyl*-1 : 2 : 3 : 4-*tetrahydrophenanthrene*, m. p. 66—67°, by stannic chloride or phosphoric oxide, and the cyclic ketone afforded 1-*methyl*-8-*isopropyl*-3 : 4-*dihydrophenanthrene* (III), m. p. 72—73°, on successive treatment with methylmagnesium iodide and formic acid. The dihydro-compound was smoothly dehydrogenated by chloranil to 1-*methyl*-8-*isopropylphenanthrene*, m. p. 100·5—101°, which is identical with the hydrocarbon obtained by the dehydrogenation of totarane (Short and Stromberg, *J.*, 1937, 510). The consequences of this identity on the structure of totarol are discussed in a forthcoming communication.

Experimental.

1-*Bromo*-8-*isopropenylnaphthalene*.—A mixture of acetone (6 c.c., 1·6 mols.), ether (15 c.c.), and benzene (6 c.c.) was added to a Grignard solution prepared from 1 : 5-dibromonaphthalene (15 g.) (Fieser and Riegel, *loc. cit.*), magnesium (1·5 g.), ether (60 c.c.), and benzene (12 c.c.), and the mixture was boiled for an hour. The unsaturated *bromo*-compound (9·4 g., 73%), b. p. 140—170°/3 mm., was isolated in the usual way and a middle fraction, b. p. 160—165°/3 mm., was analysed (Found : Br, 32·1. $C_{13}H_{11}Br$ requires Br, 32·4%).

5-*Nitro*-1-*chloromethylnaphthalene*.—1-Nitronaphthalene (26·5 g.), paraformaldehyde (27·5 g., 0·55 mol.), anhydrous zinc chloride (27·5 g.), and concentrated hydrochloric acid (15 g.) were stirred at 65—70° for 20 hours, a current of hydrogen chloride being passed into the mixture. The product was poured into water, and the solid was then collected, washed with water to neutrality, pressed to remove oily impurities, and recrystallised twice from carbon tetrachloride, giving 5-nitro-1-chloromethylnaphthalene, m. p. 96—96°, in 57% yield. The preparation was repeated several times, using up to 850 g. of nitronaphthalene per batch, and approx. 1 kg. of the chloromethyl compound was prepared, the

* Part X, *J.*, 1939, 767.

average yield being 54%. The I.G. Farbenindustrie (B.P. 473,523) records m. p. 96—97° and states that the yield is 74%.

5-Nitro-1-hydroxymethylnaphthalene.—The chloromethyl compound was suspended in approximately 2*N*-sodium carbonate (1·8 mols.) and, after being boiled under reflux for 48 hours, the mixture was cooled, and the solid was washed with water and crystallised from chloroform giving *5-nitro-1-hydroxymethylnaphthalene*, m. p. 128—129° (Found: C, 65·2; H, 4·35. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·4%). The average yield was 65%. 5-Nitro-1-chloromethylnaphthalene (10 g.), anhydrous sodium acetate (5 g., 1·3 mols.), and acetic anhydride (50 c.c., 11·5 mols.) were boiled for 3 hours and worked up. Crystallisation of the solid from ethanol afforded *5-nitro-1-acetoxymethylnaphthalene* (67%), m. p. 90° (Found: C, 63·2; H, 4·7; N, 6·15, 5·9. $C_{13}H_{11}O_4N$ requires C, 63·7; H, 4·5; N, 5·7%).

5-Nitro-1-naphthaldehyde and 5-Nitro-1-naphthoic Acid.—(*a*) A solution of chromic anhydride (2·5 g.; equiv. to 1·5 atoms of oxygen) in hot acetic acid (75 c.c.) was added during 1½ hour to a stirred solution of the preceding alcohol (5 g.) in acetic acid (50 c.c.), the temperature being kept at 65—70° during the addition and for an hour subsequently. The solution was concentrated to 15 c.c. below 80°, and the residue was washed with dilute hydrochloric acid and water. Extraction with dilute aqueous sodium carbonate removed 5-nitro-1-naphthoic acid (1·1 g., 21%), m. p. 235—237°, and crystallisation of the residue from chloroform then gave 5-nitro-1-naphthaldehyde (1·3 g., 27%), m. p. 134—136°. The *semicarbazone* had m. p. 301—304° (decomp.) (Found: N, 22·4. $C_{12}H_{10}O_3N_4$ requires N, 21·7%). Ruggli and Burckhardt (*loc. cit.*), who nitrated 1-naphthaldehyde, record 136—137° and 236—237° as the m. p. of the nitro-aldehyde and the nitro-acid, respectively, whilst Ekstrand (*J. pr. Chem.*, 1888, **38**, 241) states that the acid has m. p. 239°. When the alcohol (60 g.) was dissolved in acetic acid (900 c.c.) and oxidised at 65—70° with chromic anhydride (75 g.; equiv. to 2·5 atoms of oxygen) in acetic acid (2250 c.c.) no aldehyde was produced and the yield of nitro-acid, m. p. 237—239°, was 51 g. (53%).

(*b*) When a solution of potassium permanganate (4·3 g.; equiv. to 2·05 atoms of oxygen) in water (100 c.c.) was gradually added to a boiling suspension of 5-nitro-1-chloromethylnaphthalene (4·4 g.) in 17% aqueous sodium hydroxide (100 c.c.; 26 mols.) the product consisted of 5-nitro-1-naphthoic acid (0·9 g., 21%) and 5-nitro-1-hydroxymethylnaphthalene (1·8 g. 44%).

5-Amino-1-naphthoic Acid.—The nitro-acid (7·4 g.) was reduced with a solution of ferrous sulphate heptahydrate (67·5 g., 7·1 mols.) in water (225 c.c.) in the presence of concentrated ammonia (150 c.c.), and the crude amino-acid (5·2 g., 82%) was crystallised from ethanol giving *5-amino-1-naphthoic acid* in orange needles, m. p. 201—202° (Found: N, 7·1. $C_{11}H_9O_2N$ requires N, 7·4%). The *hydrochloride* separated from alcohol in orange needles, m. p. 278—280° (decomp.; rapid heating) (Found: N, 6·2. $C_{11}H_{10}O_2NCl$ requires N, 6·3%).

1-Naphthyl Methyl Ketone.—The ketone was prepared by adding a solution of aluminium chloride and acetyl chloride in ethylene chloride to a solution of naphthalene in ethylene chloride at 30—35° and stirring the solution at this temperature for 2—3 hours, according to Baddeley's general directions (*J.*, 1949, S 99). Pure 1-naphthyl methyl ketone has m. p. 10·5° (Lock, *Monatsh.*, 1943, **74**, 77), and no ketone melting below 0° was employed in the preparation of 1-naphthoic acid. A fraction of the ketone, b. p. 132—134°/2 mm., usually melted in the range 2—4°, whereas a higher fraction, b. p. 134—136°/2 mm., melted in the range −5° to 0° and contained some 2-naphthyl methyl ketone. If the higher-boiling fraction was not rejected some sodium 2-naphthoate separated during the preparation of 1-naphthoic acid (below). When naphthalene, aluminium chloride, and acetyl chloride were employed in the molecular ratio 1 : 2 : 2, 2000 g. of naphthalene afforded 2014 g. (58%) of ketone having m. p. >0°, and when the ratio was 1 : 1·1 : 1·3, 676 g. of naphthalene gave 574 g. (64%) of ketone of this quality. The yield of ketone, b. p. 134—136°/2 mm. was *ca.* 10%.

1-Naphthoic Acid.—1-Naphthyl methyl ketone was oxidised with alkaline sodium hypochlorite essentially according to the method of Fieser, Newman, and Holmes (*J. Amer. Chem. Soc.*, 1936, **58**, 1055. Compare Newman and Holmes, *Org. Synth.*, 1937, **17**, 65; Coll. Vol. II, 1943, 428). A solution 1·6*M*. with respect to sodium hypochlorite and 0·54*M*. with respect to sodium hydroxide was prepared from technical sodium hypochlorite solution (2·6—2·8*M*.), sodium hydroxide and water, and 3125 c.c. of this solution (containing 5 mols. of sodium hypochlorite and 1·7 mols. of sodium hydroxide) were used for the oxidation of 170 g. of the ketone. A large flask is necessary since there is considerable frothing during the liberation of chloroform, and efficient stirring is essential. Metal stirrers should not be used since they cause decomposition of the hypochlorite and promote the formation of chloronaphthoic acid. An exothermic reaction occurred when the mixture was stirred vigorously at 55° and the temperature was maintained at 60—65° by occasionally cooling in ice-water during this phase (40 minutes). The mixture was stirred at 60—65° for another 30 minutes and excess of hypochlorite was then destroyed by adding aqueous sodium hydrogen sulphite. (If the ketone was contaminated with the 2-isomer a little sodium 2-naphthoate separated on cooling the solution.) The solution was acidified with concentrated hydrochloric acid, and the solid was collected, washed with water, and crystallised once from aqueous ethanol. The 1-naphthoic acid had m. p. 149—152° and was sufficiently pure for use in subsequent operations; the pure acid has m. p. 160°. 1500 G. of 1-naphthoic acid were prepared in this way and the average yield was 87%.

5-Bromo-1-naphthoic Acid.—An improved yield of this acid was obtained by modifying Kerkhof's method (*loc. cit.*). A solution of 1-naphthoic acid (200 g.) in glacial acetic acid (500 c.c.) was heated on the steam-bath and stirred during the addition of bromine (60 c.c., 1·01 mols.). A yellow solid separated during the addition (1 hour), and, after being heated and stirred for another 1½ hours and kept overnight at room temperature, the solid was crystallised from acetic acid (2000 c.c.). The average yield in the preparation of 920 g. of bromo-acid was 56% and this product, which melted within the range 252—255°, was used in subsequent experiments. Recrystallisation from acetic acid and methanol raised the m. p. to 256—256·5°; Kerkhof (*loc. cit.*) records m. p. 261°, and Ruggli and Preuss (*Helv. Chim. Acta*, 1941, **24**, 1359), m. p. 245—247°. A complex mixture of bromo-acids was precipitated when the filtrates were diluted with water.

Methyl 5-Bromo-1-naphthoate.—(*a*) Methyl sulphate (240 c.c., 4·2 mols.) was slowly added to a stirred solution of the bromo-acid (150 g.) and sodium hydroxide (30 g., 1·25 mols.) in water (600 c.c.) and

methanol (600 c.c.). The mixture was stirred at room temperature for 3 hours, heated to the b. p. on the steam-bath, cooled, and made alkaline with aqueous sodium carbonate. The solid was collected, and unchanged acid (43%), m. p. 251—254°, was recovered from the alkaline solution. After being washed with water and dried, the crude ester (49%) had m. p. 64—65°, and crystallisation from methanol afforded *methyl 5-bromo-1-naphthoate* in needles, m. p. 66—67° (Found: Br, 30·0. $C_{12}H_9O_2Br$ requires Br, 30·2%). The ester sublimes readily but can be distilled; b. p. 268—274°/215 mm., 170—175°/3·5 mm. (*b*) When dry powdered potassium 5-bromo-1-naphthoate (5·8 g.) and methyl sulphate (3 c.c., 1·6 mols.) were heated at 200—210° for 1 hour the yield of ester was 3·3 g. (62·5%), but no acid was recovered.

1-*Bromo*-5-iso*propenylnaphthalene.*—A solution of methyl 5-bromo-1-naphthoate (26·5 g.) in ether (1200 c.c.) was added during 1½ hours to an ice-cold solution of methylmagnesium iodide (2·4 mols.), prepared from magnesium (57·5 g.), methyl iodide (148 c.c.), and ether (400 c.c.). After being stirred overnight at room temperature and boiled for 1 hour, the complex was decomposed and the crude product was distilled with powdered potassium hydrogen sulphate (50 g.) giving the crude bromonaphthalene, b. p. 140—150°/3—4 mm. The average yield was 54%, and there was occasionally a fraction of higher b. p. which solidified on cooling and consisted of unchanged methyl 5-bromo-1-naphthoate (5—10%). A middle fraction, b. p. 138—140°/2 mm., of the 1-*bromo*-5-iso*propenylnaphthalene* was analysed (Found: C, 62·7; H, 4·5. $C_{13}H_{11}Br$ requires C, 63·1; H, 4·5%). The *picrate* separated from alcohol in yellow needles, m. p. 94—95° (Found: N, 9·0. $C_{13}H_{11}Br,C_6H_3O_7N_3$ requires N, 8·8%).

2-5′-iso*Propenyl*-1′-*naphthylethyl Alcohol.*—1-Bromo-5-*iso*propenylnaphthalene is reluctant to react with magnesium, and when methyl iodide or ethyl bromide was used as entrainer, subsequent reaction with ethylene oxide afforded very low yields of the desired alcohol, and hydrocarbons were produced in considerable quantity, analyses suggesting that bromine had been partly replaced by methyl and ethyl, respectively. When Gilman and Kirby's iodine-activated magnesium (*Rec. Trav. chim.*, 1935, **54**, 577) was used, a 43% yield of the alcohol was obtained but it was not possible to use a small amount of this activated magnesium to promote reaction of the halide with ordinary magnesium. Much better results were obtained by using preformed ethylmagnesium bromide as catalyst, the reaction being carried out in an atmosphere of dry nitrogen.

A solution of 1-bromo-5-*iso*propenylnaphthalene (175 g.) in dry ether (700 c.c.) was added during 4 hours to an ice-cold, stirred suspension of magnesium in ethereal ethylmagnesium bromide prepared from magnesium (36 g., 2·1 atoms), ethyl bromide (52·5 c.c., 1 mol.), and ether (440 c.c.). After the mixture had been stirred overnight and boiled under reflux for 1 hour, it was cooled to 0°, and a 25% (w/v) solution of ethylene oxide in dry benzene (520 c.c.; 4·2 mols.) was introduced during 3 hours. The mixture was then boiled under reflux for an hour, the ether was removed by distillation, and the residue, still containing most of the benzene, was cooled and decomposed with ice-cold dilute hydrochloric acid. The alcohol was purified by distillation, the fraction, b. p. 152—158°/1 mm., being collected (average yield, 74%). 2-5′-iso*Propenyl*-1′-*naphthylethyl alcohol* was a colourless, viscous liquid; a fraction, b. p. 153—154°/1 mm., was analysed (Found: C, 83·4, 83·6; H, 7·3, 7·4. $C_{15}H_{16}O$ requires C, 84·9; H, 7·55%). 2-5′-iso*Propenyl*-1′-*naphthylethyl* p-*diphenylylcarbamate* crystallised from benzene–light petroleum in colourless needles, m. p. 147—148° (Found: C, 82·3; H, 6·2; N, 3·5. $C_{32}H_{31}O_2N$ requires C, 82·5; H, 6·15; N, 3·4%). Some of the earlier preparations of the alcohol afforded a small fraction, b. p. 165—220°/2 mm., which solidified and afforded crystals, m. p. 183—184°, after crystallisation from alcohol, probably of 5 : 5′-*diisopropenyl*-1 : 1′-*dinaphthyl* (Found: C, 92·7; H, 6·5. $C_{26}H_{26}$ requires C, 92·9; H, 7·0%).

2-5′-iso*Propyl*-1′-*naphthylethyl Alcohol.*—The unsaturated alcohol (75 g.) was readily reduced when dissolved in methanol (750 c.c.) and shaken with palladium–strontium carbonate (30 g.; 1·2% Pd) in hydrogen at room temperature and atmospheric pressure. Absorption of hydrogen was complete in 5 hours and the average yield of alcohol, m. p. 60—62°, b. p. 158—164°/1·5 mm., was 74%. 2-5′-iso*Propyl*-1′-*naphthylethyl alcohol* separated from light petroleum (b. p. 40—60°) in cubes, m. p. 63—64° (Found: C, 83·7; H, 8·1. $C_{15}H_{18}O$ requires C, 84·1; H, 8·4%). 2-5′-iso*Propyl*-1′-*naphthylethyl* p-*diphenylylcarbamate* had m. p. 161° (Found: C, 81·6; 81·8; H, 6·5, 6·55; N, 3·7. $C_{32}H_{33}O_2N$ requires C, 82·1; H, 6·6; N, 3·4%), and 2-5′-iso*propyl*-1′-*naphthylethyl acetate* had b. p. 164—166°/1 mm., m. p. 33—34° (Found: C, 79·4; H, 7·9. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%).

2-5′-iso*Propyl*-1′-*naphthylethyl Bromide.*—Phosphorus tribromide (2·2 c.c., 0·5 mol.) was added to a solution of the alcohol (10 g.) in carbon tetrachloride (10 c.c.) at 50°, and, after being kept at 50—60° for ½ hour, the solution was poured into ice-water. The *bromide* had b. p. 131—135°/0·2 mm., and separated from light petroleum (b. p. 40—60°) in plates, m. p. 41—42° (Found: C, 65·9, 65·75; H, 6·3, 6·0; Br 29·0. $C_{15}H_{17}Br$ requires C, 65·0; H, 6·1; Br, 28·9%). The average yield was 50·5%.

2-5′-iso*Propyl*-1′-*naphthylethylmalonic Acid.*—A solution of ethyl malonate (81 g., 2 mols.) in dry xylene (130 c.c.) was added to a sodium methoxide solution prepared from sodium (7 g., 1·2 atoms) and methanol (100 c.c.), and most of the solvents was removed by distillation under reduced pressure below 80°. A solution of the preceding bromide (70 g.) in xylene (115 c.c.) was then added slowly with stirring, and the temperature was slowly raised to 140—150° (oil-bath). After 16 hours at this temperature the products were isolated: 45% of the ethyl malonate was recovered and the average yield of the substituted malonic ester, b. p. 190—195°/0·5 mm., was 59%. A solution of the malonic ester (10 g.) in methanol (10 c.c.) was added to a solution of potassium hydroxide (8·15 g., 4·4 mols.) in water (10 c.c.), and, when the vigorous reaction had subsided, water (40 c.c.) was added, and the hydrolysis was completed by heating the solution on the steam-bath for 3 hours. The crude malonic acid, m. p. 149—151° (decomp.), was isolated, the average yield being 86%. Recrystallisation of this from acetic acid or benzene afforded 2-5′-iso*propyl*-1′-*naphthylethylmalonic acid* in white plates, m. p. 151—152° (decomp.) (Found: C, 72·3; H, 6·7. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%).

γ-5-iso*Propyl*-1-*naphthylbutyric Acid.*—This acid was obtained in 91% yield when the malonic acid was heated at 155—165° for 2 hours and the residue was crystallised from light petroleum (b. p. 60—80°). The pure *acid* crystallised from light petroleum in plates or needles, m. p. 120—121° (Found: C, 78·7, 79·0; H, 7·8, 7·8%; *M*, by titration, 256, 255. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%; *M*, 256).

1-*Keto*-8-*isopropyl*-1 : 2 : 3 : 4-*tetrahydrophenanthrene*.—(*a*) The butyric acid (10 g.), phosphoric oxide (50 g., 9 mols.), and benzene (150 c.c.) were heated under reflux for 3 hours, and the product was worked up as described in previous parts of the series. The neutral fraction, b. p. 165—172°/0·3 mm., solidified on cooling giving the crude ketone, m. p. 81—84° (36%), crystallisation of which from light petroleum afforded 1-*keto*-8-*isopropyl*-1 : 2 : 3 : 4-*tetrahydrophenanthrene* in colourless needles, m. p. 86—87° (Found: C, 85·3; H, 7·6. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%). The *semicarbazone* crystallised from alcohol in colourless prisms, m. p. 246—247° (decomp.) (Found: N, 14·2. $C_{18}H_{21}ON_3$ requires N, 14·2%). The crude ketone isolated from the mother liquors afforded the same semicarbazone, showing that no isomeric ketone is produced in the ring closure. Only a trace of unchanged acid was recovered. (*b*) A mixture of the butyric acid (3 g.) and stannic chloride (3·0 c.c., 2·8 mols.) was heated at 105—110° for 1½ hours with frequent shaking, cooled, and decomposed with ice-cold dilute hydrochloric acid. After removal of unchanged acid, m. p. 117—119° (15%), the ketone (60%) solidified without distillation and was obtained pure, m. p. and mixed m. p. 86—87°, after one crystallisation from light petroleum.

1-*Methyl*-8-*isopropyl*-3 : 4-*dihydrophenanthrene*.—A solution of the cyclic ketone (5 g.) in ether (70 c.c.) was added at room temperature to a solution of methylmagnesium iodide (3 mols.), prepared from magnesium (1·5 g.), methyl iodide (4·3 c.c.), and ether (50 c.c.), and, after being boiled under reflux for 3 hours, the product was isolated. The dehydration of the crude carbinol was completed by boiling it for ½ hour with 100% formic acid (10 c.c.) and the crude hydrocarbon, b. p. 165—170°/1 mm., was purified by crystallisation from methanol, giving white plates of 1-*methyl*-8-*isopropyl*-3 : 4-*dihydrophenanthrene* (3·3 g.; 67%), m. p. 72—73° (Found: C, 91·5; H, 8·7. $C_{18}H_{20}$ requires C, 91·5; H, 8·5%).

1-*Methyl*-8-*isopropylphenanthrene*.—A solution of the dihydrophenanthrene (1·5 g.) and chloranil (1·57 g., 1 mol.) in sulphur-free xylene (7 c.c.) was boiled under reflux until no colour reaction for chloranil was obtained (20 hours). The solution was cooled to 0° and filtered from tetrachloroquinol, and the filtrate was diluted with ether, washed with 5% aqueous potassium hydroxide, dried ($MgSO_4$), and evaporated. The residue was crystallised several times from methanol (charcoal) giving 1-*methyl*-8-*isopropylphenanthrene* (0·4 g.) in white plates, m. p. 100·5—101° (Found: C, 92·0; H, 7·8. $C_{18}H_{18}$ requires C, 92·3; H, 7·7%). The material recovered from the mother liquors was distilled from sodium under reduced pressure, and the fraction, b. p. 180—185°/2 mm., which solidified on cooling, was crystallised from ethanol giving 0·51 g. of hydrocarbon, m. p. 99—100° (total yield, 61%). The *picrate* crystallised from alcohol in orange-yellow needles, m. p. 142—142·5° (Found: C, 62·9; H, 4·4; N, 9·25. $C_{18}H_{18}C_6H_3O_7N_3$ requires C, 62·3; H, 4·5; N, 9·1%), and the *styphnate* in yellow needles, m. p. 152·5—153° (Found: C, 61·2, 61·1; H, 4·5, 4·4; N, 9·0. $C_{18}H_{18}C_6H_3O_8N_3$ requires C, 60·2; H, 4·4; N, 8·8%). Oxidation of the hydrocarbon (0·2 g.) in acetic acid (3 c.c.) with chromic anhydride (0·26 g. in 0·5 c.c. of water and 1·5 c.c. of acetic acid), the mixture being heated finally on the steam-bath for 10 minutes, afforded 1-*methyl*-8-*isopropylphenanthra*-9 : 10-*quinone* which separated from acetic acid in orange rods, m. p. 163·5—164° (Found: C, 81·4; H, 6·1. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%). A specimen of the quinone was converted into 1′-*methyl*-4″-*isopropyl*-1 : 2 : 3 : 4-*dibenzphenazine*, which crystallised from ethanol–chloroform in pale yellow rods, m. p. 153·5—154° (Found: N, 8·05. $C_{32}H_{28}N_2$ requires N, 8·3%).

The authors are indebted to Messrs. J. K. Davison, R. Staniforth, and L. A. Watson for experimental assistance and to Miss C. Coleman and Miss F. Skidmore for the semi-microanalyses.

Research Laboratories, Messrs. Boots Pure Drug Co. Ltd., Nottingham. [*Received, December 28th*, 1949.]

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205. *Hydrogen Chloride–Aluminium Chloride as an Agent of Isomerisation.*

By G. Baddeley.

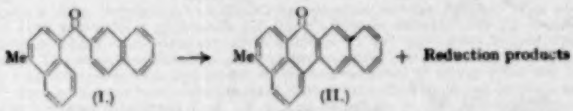
Hydrogen chloride catalyses the Scholl reaction and the intramolecular migration of alkyl groups in phenol homologues, aromatic ketones, and aromatic hydroxy-ketones, in the presence of aluminium chloride. These reactions do not occur, or occur at greatly reduced rates, when a stream of dry oxygen or nitrogen is passed through the reaction mixtures. The significance of these results is discussed.

Many reactions effected by aluminium chloride and other Friedel–Crafts reagents do not occur in the absence of hydrogen chloride or traces of water—for instance, the polymerisation of olefins in the presence of aluminium chloride (Thomas and Carmody, *J. Amer. Chem. Soc.*, **1933**, **55**, 3854; Ipatieff and Grosse, *ibid.*, 1936, **58**, 913; Waterman and Leendertse, *J. Inst. Petr. Tech.*, 1938, **24**, 16). Polymerisation of *iso*butene by boron fluoride requires the presence of moisture or, in general, a substance YH capable of forming a strong acid BF_3,YH (A. G. Evans and Polanyi, *J.*, 1947, 252). Other Friedel–Crafts catalysts are subject to the same limitation (Plesch, Polanyi, and Skinner, *J.*, 1947, 257). Reactions of olefins with *iso*paraffins and aromatic hydrocarbons (Ipatieff and Grosse, *J. Amer. Chem. Soc.*, 1935, **57**, 1616; *J. Org. Chem.*, **1937**, **1**, 559), isomerisation of paraffins and *cyclo*paraffins (Thomas, "Anhydrous Aluminium Chloride in Organic Chemistry," Reinhold, **1941**; Leighton and Heldman, *J. Amer. Chem. Soc.*, **1943**, **65**, 2276; Heldman, *ibid.*, 1944, **66**, 1786), and decomposition of paraffins into higher- and

lower-boiling hydrocarbons (Ipatieff and Grosse, *Ind. Eng. Chem.*, 1934, **26**, 461) are other reactions effected by aluminium chloride in the presence of hydrogen chloride.

Reversible intramolecular migration of methyl groups in phenol homologues (*J.*, 1943, 527), and irreversible intramolecular migration of methyl and ethyl groups in aromatic ketones (*J.*, 1944, 232) and in aromatic hydroxy-ketones (*J.*, 1943, 273), were caused by aluminium chloride in the presence of hydrogen chloride normally generated when the reactants were brought together in such a manner as to provide homogeneous reaction mixtures. To show whether hydrogen chloride promotes these reactions it is necessary to displace it from the reaction mixtures and to observe whether the rates of isomerisation are adversely affected.

4-Methyl-1 : 2′-dinaphthyl ketone (I), in solution in chlorobenzene, is readily converted (70% yield) at room temperature into 4-methyl-9′ : 10′-ben*zmeso*benzanthrone (II) by the

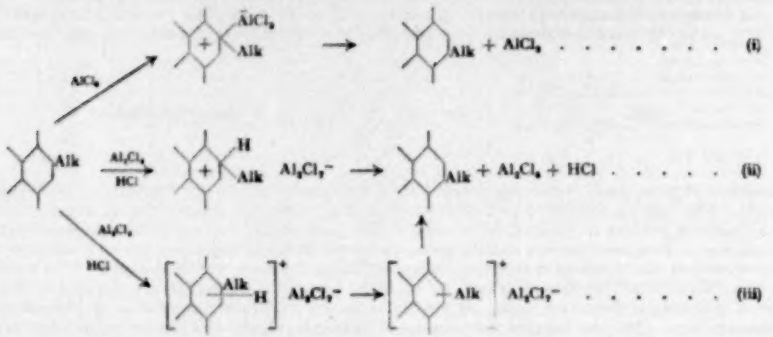


addition of more than a molecular proportion of aluminium chloride (cf. Buckley, *J.*, 1945, 561, 564). This can be considered as a disproportionation; when dry oxygen was passed through the reaction mixture in an attempt to improve the yield of (II), hydrogen chloride was swept from the mixture, and reaction did not occur; a stream of dry nitrogen had the same effect and in each case the reaction commenced when hydrogen chloride was introduced. The more conventional Scholl reaction, in which, for example, 1-benzoylnaphthalene is converted in 70% yield into benzanthrone by fusion with more than two molecular proportions of aluminium chloride at *ca.* 125°, also requires the presence of hydrogen chloride and did not occur when dry oxygen or nitrogen was passed through the molten mixture; addition of sodium chloride and consequent formation of $NaAlCl_4$ did not promote the reaction. These observations, a full account of which will be submitted in a later paper, indicated not only that the presence of hydrogen chloride is essential for the occurrence of the Scholl reaction, but also that a stream of dry nitrogen or oxygen can effectively remove hydrogen chloride from liquid mixtures containing aluminium chloride.

An expeditious and decisive method was now available for demonstrating whether the presence of hydrogen chloride is also necessary in the intramolecular migration of alkyl groups in the benzene derivatives indicated above. As a result of the earlier work on the kinetics of these reactions, homogeneous reaction mixtures of low viscosity were obtained at temperatures well below those required for isomerisation; almost all the hydrogen chloride was swept out with dry nitrogen, and the reaction mixtures were then kept at temperatures adequate for isomerisation. For example, after hydrogen chloride had been removed from a mixture of *p*-cresol and aluminium chloride at 85°, isomerisation did not occur at 135°. Under comparable conditions, but in the presence of hydrogen chloride, the 2 : 3 equilibrium mixture of *p*- and *m*-cresol was obtained. The isomerisation of acetophenone homologues is accompanied by some decomposition and consequent evolution of hydrogen chloride: a stream of dry nitrogen markedly increased the rate of decomposition of 2 : 4-dimethylacetophenone, and hydrogen chloride could not be rigorously excluded at 135°, the temperature of isomerisation. The continuous removal of hydrogen chloride had, however, an adverse effect on the rate of isomerisation. Aromatic *o*-hydroxy-ketones are more resistant to decomposition and 6-hydroxy-2 : 4-dimethylpropiophenone, which can be quantitatively converted into 6-hydroxy-3 : 4-dimethylpropiophenone, did not isomerise after hydrogen chloride had been removed. As all these isomerisations require the presence of hydrogen chloride, it is necessary to state that the reaction mixtures employed in the earlier kinetic studies were in an atmosphere of hydrogen chloride at atmospheric pressure.

So far it has not been possible to demonstrate that hydrogen halide promotes the isomerisation of *p*-xylene in the presence of aluminium halide, as aluminium halide does not combine with the hydrocarbon in the absence of a third component such as hydrogen halide. Norris *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 1163, 2131; 1940, **62**, 1298, 1428) have prepared ternary complexes by passing hydrogen halide into a mixture of aromatic hydrocarbon and aluminium halide and, although they appear to have converted these into binary complexes by elimination of hydrogen halide under reduced pressures, Mr. Voss has found in this laboratory that a stream of dry nitrogen does not wholly remove the hydrogen bromide from its ternary complexes with

aluminium bromide and *m*- or *p*-xylene. Aluminium and hydrogen halides do not interact and their combined action on aromatic hydrocarbons, which at low temperatures exhibit weak basic properties towards hydrogen chloride (Brown and Brady, *ibid.*, 1949, **71**, 3573), can be represented by: $ArH + HX + Al_2X_6 \longrightarrow ArH_2^+ + Al_2X_7^-$. This is in accord with the hydrogen exchange observed when deuterium chloride is passed into a mixture of benzene and aluminium chloride (Kenner, Polanyi, and Szego, *Nature*, 1935, **135**, 267), and when applied to the migration of alkyl groups in benzene derivatives leads to mechanism (ii) or (iii) instead of (i) which was previously proposed.



As previously emphasised (Baddeley, *loc. cit.*), the essential feature of all these isomerisations is the formation of a carbonium ion, followed by a rearrangement of the Wagner and Meerwein type:

and subsequently the isomerisation of paraffins and *cyclo*paraffins has been shown to involve intramolecular rearrangement of carbonium ions. Traces of alkyl or *cyclo*alkyl halide in the presence of aluminium halide or of olefin in the presence of both aluminium and hydrogen halides (Pines *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 153; 1948, **70**, 1742) or of sulphuric acid (Burwell and Gordon, *ibid.*, 1948, **70**, 3128) provide carbonium ions (R^+) which initiate chain reactions resulting in isomerisation:

$$R^+ + AlkH \longrightarrow RH + Alk^+$$
$$Alk^+ \rightleftharpoons Alk_1^+$$
$$Alk_1^+ + AlkH \rightleftharpoons Alk_1H + Alk^+$$

This mechanism is in accord with the rapid conversion of *tert.*-butyl bromide and *iso*pentane into *iso*butane and *tert.*-amyl bromide in the presence of aluminium bromide (Bartlett, Condon, and Schneider, *ibid.*, 1944, **66**, 1531), and with the observation (Ipatieff, *ibid.*, 1949, **71**, 749) that benzene, by combining with alkyl cations, inhibits the isomerisation of methyl*cyclo*pentane by the combined action of *sec.*-butyl bromide and aluminium bromide. Aluminium and hydrogen bromides do not combine in *n*-butane or *n*-hexane (Fontana and Herold, *ibid.*, 1948, **70**, 2281) and it is not surprising therefore that hydrogen halide does not promote the interconversion of *cyclo*hexane and methyl*cyclo*pentane in the presence of aluminium halide (Stevenson and Beeck, *ibid.*, 1948, **70**, 2890).

Experimental.

A mixture of *p*-cresol (64 g.) and freshly sublimed aluminium chloride (180 g.) was kept at 120—125° (oil-bath) for 15 minutes and subsequently at 90° for 30 minutes. The clear pale brown liquid was decanted from undissolved chloride into two vessels which were placed in a thermostat at 90°. One was fitted with a drying ($CaCl_2$) tube and the other (*A*) with a sintered-glass gas distributor through which dry (P_2O_5) nitrogen at the temperature of the thermostat was passed at a rate of 30 c.c. per minute. The escaping gases were passed through a large plug of glass wool to remove aluminium chloride, a

drying ($CaCl_2$) tube, and a bubbler containing water. After several hours, the gases escaping in the following hour neutralised 1·0 c.c. of N/10-sodium hydroxide. The reaction mixtures were then kept at 135° for 9 hours. The amount of hydrogen chloride in the escaping gases remained small. The mixtures were decomposed with ice and dilute hydrochloric acid, and the cresol isolated. That obtained from the mixture (*A*) was nearly pure *p*-cresol (m. p. 31°; mixed m. p. 33°); the other did not solidify at 0° and contained *m*- (60%) and *p*-cresol (40%) (bromate analysis, *loc. cit.*).

A mixture of 2 : 4-dimethylacetophenone (50 g.) and aluminium chloride (100 g.) was heated at 100° for 15 minutes and the homogeneous solution decanted into two vessels. Subsequent procedure was as above. At 135° the mixture (*B*), from which considerable quantities of hydrogen chloride were continuously removed by nitrogen, became much darker than the other. The latter, on decomposition with ice and dilute hydrochloric acid, provided 3 : 4-dimethylacetophenone (semicarbazone, m. p. and mixed m. p. 235°) which contained very little initial ketone (separated by the greater solubility of its semicarbazone in ethanol). The product from (*B*) contained a considerable amount of tar, and the steam-volatile material was a mixture of approximately equal amounts of 2 : 4- and 3 : 4-dimethylacetophenone.

The procedure with 6-hydroxy-2 : 4-dimethylpropiophenone was similar. The reaction mixture was obtained from *m*-5-xylenyl propionate (55 g.), aluminium chloride (126 g.), and sodium chloride (12 g.). Samples which were removed after 5 hours at 85° gave pure 6-hydroxy-2 : 4-dimethylpropiophenone. The nitrogen emitted in an hour now contained an amount of hydrogen chloride which neutralised 0·5 c.c. of N/10-sodium hydroxide, which was increased to 15 c.c. when the temperature was raised to 140°, the reaction mixture becoming much darker than when hydrogen chloride was not removed. These mixtures provided 6-hydroxy-2 : 4- (m. p. and mixed m. p. 75°) and 6-hydroxy-3 : 4-dimethylpropiophenone (m. p. and mixed m. p. 60°) respectively. The former was separated from tar by distillation with steam.

The author is indebted to Professor J. Kenner, F.R.S., for many helpful discussions.

THE COLLEGE OF TECHNOLOGY, MANCHESTER, 1. [*Received, January 5th*, 1950.]

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206. *Aromatic Sulphonation. Part I. The Ionisation Constants of* p-*Nitrotoluene, Nitrobenzene, and* p-*Chloronitrobenzene, and the Acidity Function of Oleum.*

By J. C. D. BRAND.

The ionisation constants (pK_a) of *p*-nitrotoluene (−10·28), nitrobenzene (−11·26), and *p*-chloronitrobenzene (−11·49) have been determined spectrometrically, and the acidity-function scale of sulphuric acid has been extended into oleum containing up to 14% of sulphur trioxide.

AROMATIC mononitro-compounds are weak, although not unobservably weak, bases and their ionisation can be measured in a strongly acidic medium. This basic property was first noticed by Hantzsch (*Z. physikal. Chem.*, 1908, **65**, 41) who found that *p*-nitrotoluene lowered the freezing point of sulphuric acid more than did a non-electrolyte and concluded that the *p*-nitrotoluene was partly converted into an oxonium salt. Cherbuliez (*Helv. Chim. Acta*, 1923, **6**, 281) and Masson (*J.*, 1931, 3200) showed independently that the conductivity of anhydrous sulphuric acid was enhanced by dissolved nitrobenzene and successfully prepared a crystalline addition product, regarded as the hydrogen sulphate, $[C_6H_5{\cdot}NO_2H]^+SO_4H^-$. The ionisation of nitrobenzene in sulphuric acid was confirmed cryoscopically by Treffers and Hammett (*J. Amer. Chem. Soc.*, 1937, **59**, 1708), and Gordy and Stanford (*J. Chem. Physics*, 1940, **8**, 170) estimated the order of magnitude of the ionisation constant from a comparison of the frequency of the O–D stretching vibration of methyl deuteroalcohol in benzene and nitrobenzene solution.

In the present series of measurements, the degree of ionisation of *p*-nitrotoluene, nitrobenzene, and *p*-chloronitrobenzene was determined spectrometrically in media of successively increasing sulphuric acid concentration. If the ion and free base are assumed to absorb independently, the extinction coefficient (ε) of a solution containing both forms is $\varepsilon = \varepsilon_{BH^+}[BH^+] + \varepsilon_B[B]$, where ε_{BH^+} and ε_B, $[BH^+]$ and $[B]$, are respectively the extinction coefficients (at a particular wave-length) and the relative concentrations of the ion and free base. Because $[BH^+] + [B] = 1$ this equation can be written as $[B]/[BH^+] = (\varepsilon_{BH^+} - \varepsilon)/(\varepsilon - \varepsilon_B)$, which enables the indicator-ionisation ratio to be evaluated directly from the absorption measurements. The ionisation ratio is related to the ionisation constant of the base and the acidity function of the medium by the equation (Hammett, *Chem. Reviews*, 1935, **16**, 67):

$$H_0 = pK_a + \log [B]/[BH^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where K_a is the acidic ionisation constant of the ion BH^+ and H_0 is the acidity function of the

medium with respect to an uncharged base. The acidity function of sulphuric acid up to 100% has been determined (Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; Hammett and Paul, *ibid.*, 1934, **56**, 827), and by combining these results with a cryoscopic measurement of the degree of ionisation Hammett (*J. Chem. Physics*, 1940, **8**, 644) found pK_a −11 for nitrobenzene. An improved determination by the same method (Gillespie and Millen, *Quart. Reviews*, 1948, 292) * gave pK_a −11·0. The measurements now reported yield the following values for pK_a:

p-Nitrotoluene	−10·28	*p*-Chloronitrobenzene	−11·49
Nitrobenzene	−11·26		

Although the ionisation constants are in the expected order, the large effect of the *p*-methyl compared with that of the *p*-chloro-substituent is unusual. The result suggests that the transfer

Absorption spectra of p-nitrotoluene, nitrobenzene and p-chloronitrobenzene in sulphuric acid.

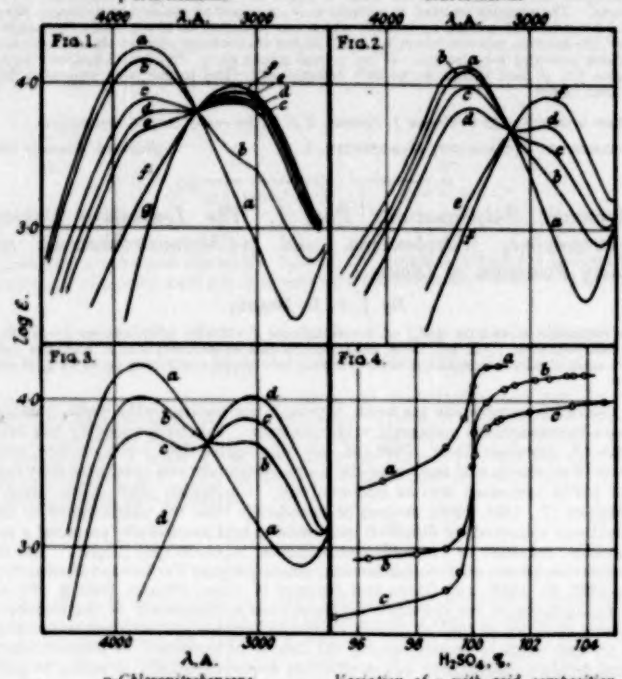

Fig. 1.	*Acid*, %
a	(calc.).
b	100·00
c	99·70
d	99·36
e	99·08
f	96·86
g	85·5

Fig. 2.	*Acid*, %
a	103·2
b	100·8
c	100·24
d	100·02
e	99·0
f	98·2

Fig. 3.	*Acid*, %
a	103·54
b	100·46
c	100·06
d	99·05

Fig. 4.	
a	*p-Nitrotoluene*
b	*p-Chloronitrobenzene*
c	*Nitrobenzene*

* The authors appear to use the original acidity-function scale, which is 0·29 unit higher (less negative) than the scale adopted in this paper (Hammett and Paul, *loc. cit.*).

TABLE I.

Evaluation of ionisation constants and acidity function (temp. 21° ± 3°).

Medium. % H_2SO_4.	Medium. % SO_3.	Extinction coefficient, ϵ.	$-\frac{1}{\epsilon}\frac{d\epsilon}{dt}$ % per min.	log [B]/[BH⁺].	Acidity function,* H_0.	Ionisation constant, pK_a.
A. *Nitrobenzene*, $\epsilon_{max.}$ = 9000, ϵ_{base} = 300 *at* λ 3650 A.						
84·6	—	203	—	—	—	—
87·6	—	231	—	—	—	—
90·76	—	254	—	—	—	—
95·10	—	329	—	2·5	−8·8	−11·3
99·02	—	507	—	1·61	−9·61	−11·22
99·07	—	511	—	1·61	−9·64	−11·25
99·10	—	505	—	1·62	−9·65	−11·27
99·50	—	686	—	1·34	−9·91	−11·25
99·51	—	686	—	1·34	−9·92	−11·26
99·53	—	693	—	1·33	−9·93	−11·26
99·55	—	664	—	1·36	−9·94	−11·30
						−11·26 ± 0·02
100·05	—	4,320	—	0·08	−11·18	—
100·06	—	4,080	—	0·10	−11·16	—
100·08	—	4,230	—	0·08	−11·18	—
100·09	—	4,350	—	0·06	−11·20	—
100·46	2·04	6,530	0·01	−0·40	−11·56	—
100·51	2·26	6,580	0·02	−0·41	−11·67	—
100·87	3·86	7,250	0·03	−0·60	−11·86	—
100·94	4·18	7,460	0·02	−0·68	−11·94	—
101·00	4·45	7,540	0·02	−0·70	−11·96	—
101·91	8·45	8,350	0·04	−1·09	−12·35	—
101·97	8·74	8,400	0·04	−1·13	−12·39	—
103·5	15·5	9,340	0·08	—	—	—
104·6	20·4	9,980	0·15	—	—	—
106·2	27·6	10,570	0·28	—	—	—
108·0	35·5	11,200	0·60	—	—	—
B. *p-Chloronitrobenzene*, $\epsilon_{max.}$ = 15,900, ϵ_{base} = 810 *at* λ 3650 A.						
94·8	—	762	—	—	—	—
96·36	—	845	—	—	—	—
98·02	—	910	—	—	—	—
99·04	—	980	—	1·94	− 9·61	−11·57
99·05	—	1,020	—	1·85	− 9·62	−11·47
99·58	—	1,280	—	1·49	− 9·97	−11·46
99·59	—	1,280	—	1·49	− 9·99	−11·48
99·99	—	3,570	—	0·65	−10·87	−11·52
100·06	—	5,970	—	0·28	−11·18	−11·46
100·07	—	6,090	—	0·27	−11·19	−11·46
100·47	—	9,570	—	−0·14	−11·66	−11·52
100·48	—	9,640	—	−0·15	−11·66	−11·51
						−11·49 ± 0·03
100·50	2·22	9,860	—	−0·18	−11·67	—
101·11	4·93	12,040	—	−0·46	−11·95	—
101·48	6·57	12,910	—	−0·61	−12·10	—
101·49	6·61	13,120	—	−0·65	−12·14	—
102·26	10·0	14,180	—	−0·89	−12·38	—
102·68	11·9	14,490	—	−0·99	−12·48	—
103·30	14·6	15,090	—	−1·24	−12·73	—
103·55	15·8	15,230	—	−1·35	−12·84	—
103·89	17·3	15,520	—	—	—	—
105·74	25·5	15,890	—	—	—	—
107·7	34·2	15,890	—	—	—	—
C. *p-Nitrotoluene*, $\epsilon_{max.}$ = 18,000, ϵ_{base} = 1850 *at* λ 3650 A.						
98·30	—	2,370	—	1·46	− 9·79	−10·27
98·73	—	4,280	—	0·75	− 9·50	−10·25
98·91	—	4,500	—	0·71	− 9·56	−10·27
99·07	—	4,780	—	0·65	− 9·64	−10·29
100·50	2·22	17,320	0·11	−1·36	−11·64	−10·31
100·92	4·08	17,890	0·26	—	—	—
						−10·28 ± 0·02

* Values of the acidity function of media for which % H_2SO_4 ⩽100·0 are taken from the Tables of Hammett and others (*loc. cit.*).

of charge by conjugation or hyperconjugation between the *p*-chloro- or *p*-methyl substituent and the point of attachment of the proton is comparatively great, certainly greater than in the corresponding isoelectronic *p*-substituted benzoate ions (which, however, are anion bases). Additional evidence on this point will be considered in the following paper. Similar effects are observed in the series of *p*-substituted acetophenones (Flexser and Hammett, *J. Amer. Chem. Soc.*, 1938, **60**, 885).

Experimental.

Materials.—*p*-Nitrotoluene, f. p. 51·5°, was purified by several recrystallisations from alcohol and from light petroleum. *p*-Chloronitrobenzene, m. p. 83°, was obtained in white crystals by recrystallisation from light petroleum and then successively from 50% nitric acid and aqueous alcohol. Nitrobenzene, f. p. 5·72°, was prepared from purified benzene, f. p. 5·5°, according to the directions of Masson (*Nature*, 1931, **128**, 726).

Fuming sulphuric acid was prepared by distillation of sulphur trioxide from commercial oleum containing potassium persulphate into concentrated sulphuric acid in an all-glass apparatus. Sulphur dioxide was oxidised by the persulphate if the strength of the oleum did not exceed about 30% of SO_3. The storage and analysis of the acids have been described previously (Brand, *J.*, 1946, 585). At wave-lengths exceeding about 2500 A. the media were sufficiently transparent to be used in thicknesses up to 10 cm.

Measurement of Extinction Coefficients.—The extinction coefficients were determined qualitatively throughout the near ultra-violet region by use of a Hilger Spekker photometer and a medium quartz spectrograph, and were evaluated by the usual equation, $\log I_0/I = \varepsilon.c.d$, where c is the concentration of solute in moles per litre and d is the thickness, in cm., of the absorbing layer. The changes in the spectrum which accompany ionisation are shown in Figs. 1—3. More accurate values of ε ($\pm 1\%$) were measured at λ 3650—3663 A. with a photoelectric apparatus, and the results are collected in Tables I and II, and Fig. 4.

Table II.

Influence of hydrogen sulphates on the acidity function of oleum.

Medium.		Added salt.		Extinction coefficient,		Acidity function,
% H_2SO_4	$[SO_3]$ concn., mol./kg.		concn., equiv./kg.	ε.	log [B]/[BH⁺].	H_0.
A. *Nitrobenzene indicator*, $\varepsilon_{max.} = 9000$, $\varepsilon_{base} = 300$ *at* λ 3650 A.						
100·46	0·26	—	—	6530 •	−0·40	−11·66
100·457	0·254	$Ba(SO_4Me)_2$	0·0830	4950	−0·06	−11·32
100·443	0·247	K_2SO_4	0·0977	4380	0·05	−11·21
100·456	0·253	K_2SO_4	0·146	3530	0·23	−11·03
100·444	0·247	$Ba(SO_4Me)_2$	0·183	2790	0·40	−10·86
100·463	0·258	K_2SO_4	0·198	2760	0·41	−10·85
100·455	0·253	K_2SO_4	0·253	1980	0·62	−10·64
100·87	0·48	—	—	7250 •	−0·60	−11·86
100·858	0·477	$Ba(SO_4Me)_2$	0·102	6180	−0·32	−11·58
100·874	0·486	K_2SO_4	0·150	5300	−0·13	−11·39
100·852	0·473	$Ba(SO_4Me)_2$	0·197	4770	−0·03	−11·29
100·844	0·469	$BaSO_4$	0·216	4820	−0·04	−11·30
100·862	0·479	K_2SO_4	0·257	3820	0·08	−11·18
100·840	0·465	K_2SO_4	0·364	2440	0·49	−10·77
100·838	0·466	K_2SO_4	0·576	1150	0·97	−10·29
B. *p-Chloronitrobenzene indicator*, $\varepsilon_{max.} = 15{,}900$, $\varepsilon_{base} = 810$ *at* λ 3650 A.						
102·68	1·49	—	—	14,490 •	−0·99	−12·48
102·57	1·43	K_2SO_4	0·0494	14,090	−0·87	−12·36
102·55	1·42	K_2SO_4	0·145	13,050	−0·63	−12·12
102·53	1·41	K_2SO_4	0·169	12,390	−0·52	−12·01
102·52	1·40	K_2SO_4	0·244	11,380	−0·37	−11·86
102·51	1·39	K_2SO_4	0·247	11,350	−0·37	−11·86
103·55	1·97	—	—	15,250 •	−1·35	−12·84
103·52	1·95	K_2SO_4	0·0988	14,560	−1·01	−12·50
103·47	1·93	K_2SO_4	0·249	13,270	−0·67	−12·16
103·39	1·89	K_2SO_4	0·488	10,460	−0·25	−11·74
103·33	1·85	K_2SO_4	0·608	8,960	−0·07	−11·56
104·44	2·47	K_2SO_4	0·246	14,440	−0·97	−12·46
104·44	2·47	K_2SO_4	0·246	14,490	−0·99	−12·48
104·35	2·42	K_2SO_4	0·479	12,510	−0·54	−12·03
104·34	2·41	K_2SO_4	0·501	11,440	−0·50	−11·99

• Table I, average.

The calibration of the apparatus was checked by using an alkaline solution of potassium chromate (von Halban, *Z. physikal. Chem.*, 1922, **100**, 221).

Calculation of Ionisation Constants and Acidity Function.—The ionisation ratio of each base in a particular medium was calculated from the photoelectric results. Independently of the changes due to ionisation, the spectra moved gradually towards longer wave-lengths as the strength of the sulphuric acid medium was increased, and in order that this effect should not unduly affect the evaluation of the ionisation ratio, values of $\varepsilon_{max.}$ and $\varepsilon_{min.}$ were chosen as close as possible to the steep portions of the curves in Fig. 4. To assist in this, the complete spectra were used to determine the range of composition of the medium within which ionisation took place. The ionisation constants were obtained from the values of the ionisation ratio of the indicators in concentrated sulphuric acid, by use of the established acidity scale, and the acidity function hence extended into fuming sulphuric acid containing up to 14% of free sulphur trioxide (Tables I and V). Table II contains measurements of the acidity function of fuming sulphuric acid in the presence of potassium sulphate, barium sulphate, and barium di(methyl sulphate).

The ionisation constant of *p*-nitrotoluene was also calculated at regular intervals of frequency from the extinction coefficients obtained from the spectra in Fig. 1 (Table III). The method of calculation is described by Flexser, Hammett, and Dingwall (*J. Amer. Chem. Soc.*, 1935, **57**, 2103). The spectrum of the ion of *p*-nitrotoluene, which was not measured because of sulphonation, has been calculated from the other curves.

p-Nitrotoluene and nitrobenzene reacted with fuming sulphuric acid and the transmission was extrapolated back to zero time. The rate of diminution of the intensity of absorption is recorded in Table I. *p*-Chloronitrobenzene was not attacked.

TABLE III.

Calculation of the ionisation constant of p*-nitrotoluene from the absorption spectrum,* λ 2500—4500 A.

Extinction coefficients.

Frequency, cm.$^{-1}$.	% H_2SO_4: H_0:	85·6 −7·9	95·86 −8·93	99·08 −9·64	99·15 −9·67	99·36 −9·80	99·70 −10·11	100·00 −10·89	$\varepsilon_{max.}$ (calc.).	$-pK_a$.
22,000		0	0	68	74	85	108	269	340	10·16
23,000		0	66	296	296	390	603	1,250	1,560	10·28
24,000		10	260	950	970	1170	1900	4,200	5,250	10·22
25,000		87	670	2250	2480	3030	4570	9,820	12,270	10·22
26,000		480	1350	4170	3890	5300	7240	14,100	17,500	10·17
27,000		1500	2360	4950	4530	6320	7820	14,100	17,300	10·13
28,000		3300	3700	5510	5380	6320	7050	10,750	12,620	10·14
29,000		5800	—	6310	6310	6460	6610	7,460	7,860	10·11
30,000		8470	—	7500	7500	7280	6920	5,180	4,350	10·10
31,000		9820	—	8510	8320	7800	7360	3,810	3,200	10·23
32,000		9890	9590	8810	8570	7850	7410	3,080	1,370	10·34
33,000		9200	8850	8130	7930	7400	6930	2,630	980	10·25
34,000		7380	7140	6700	6670	6280	5330	2,010	660	10·34
35,000		5510	5190	4980	4960	4700	3780	1,380	340	9·87
36,000		3980	—	3390	3340	3150	2510	990	260	10·45
37,000		2630	—	2190	2090	1960	1650	720	240	10·20
38,000		1800	—	1380	1310	1290	1170	600	300	9·90
39,000		1340	—	1050	1000	1010	950	650	480	9·73

Average $pK_a = 10·19 \pm 0·1$

DISCUSSION.

The acidity function of anhydrous sulphuric acid was found by Hammett and Deyrup (*loc. cit.*) to be −10·60 units. According to the results of a revised determination of the strengths of some of the more basic indicators by Hammett and Paul (*loc. cit.*) and by Braude (*J.*, 1948, 1976) the original scale should be corrected by subtracting 0·29 unit or 0·45 unit respectively. The method of Hammett and his co-workers was modified and improved by Braude, but in this paper the value adopted provisionally is −10·89, being obtained from measurements of the same type throughout.

The acidity function of 87—100% sulphuric acid may be calculated from the molecular composition, apart from a constant term. The ionisation ratio of an uncharged basic indicator is governed by the equilibrium

$$B + H_2SO_4 \overset{K}{\rightleftharpoons} BH^+ + SO_4H^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and, therefore, $(B)/(BH^+) = (SO_4H^-)/K(H_2SO_4)$, where parentheses refer to activities. This equation may be combined with equation (1) to give equation (3):

$$H_0 = pK_a + pK + \log (SO_4H^-)/(H_2SO_4) + \log(f_{BH^+} \cdot f_{H_2O,H^+}/f_B \cdot f_{H_2O_4}) \quad . \quad . \quad . \quad (3)$$

To quite a good approximation, water and molecular sulphuric acid react quantitatively to give oxonium and bisulphate ions. In mixtures in which sulphuric acid is present in molecular

excess over water, the molar ratio SO_4H^-/H_2SO_4 can, therefore, be calculated directly from the composition of the medium, and in Table IV the acidity function is evaluated in this way from the semi-theoretical equation (4):

$$H_0 = -8{\cdot}35 + \log [SO_4H^-]/[H_2SO_4] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

the constant term being obtained empirically. The agreement is poor at the top of Table IV owing to self-ionisation of the sulphuric acid, and the calculation cannot be extended to more aqueous acid because it is then certainly incorrect to assume that water is converted quantitatively into oxonium ions. The results for media between 87% and 99·8% sulphuric acid are satisfactory, however, in spite of the fact that the activity coefficients do not enter symmetrically into the final term in equation (3) which was disregarded in writing equation (4). The constancy of this term would imply that the ion-activity coefficients are practically constant throughout the range of medium composition under discussion, and this conclusion is difficult to justify, although the deviations would be on a reduced scale in a solvent of high dielectric constant. It is possible that the effect of neglecting the activity-coefficient term is fortuitously compensated by a small reversibility of the reaction between water and molecular sulphuric acid (cf. Ingold and others, *Nature*, 1946, **158**, 480), because the assumption that these components of the system react together *quantitatively* exaggerates the acidity of sulphuric acid and should, of itself, yield results more negative than those observed experimentally. Since the ionic activity coefficients would (initially) decrease from unity, the logarithm of their product would be negative and the approximation involved in writing equations (3) and (4) partly cancel one another. Nevertheless, the diminishing concentration of bisulphate ions in acids containing a small proportion of water (0·5—0·0% of H_2O) obviously accounts for the sharp rise of the acidity function in this region (cf. Lewis and Bigeleisen, *J. Amer. Chem. Soc.*, 1943, **65**, 1144).

TABLE IV.

Comparison of calculated and observed values of the acidity function (87·5—100% H_2SO_4).

Medium.		Molar ratio,	Acidity function.	
% H_2SO_4.	% H_2O.	SO_4H^-/H_2SO_4.	Calc.	Obs.*
99·9	0·1	0·0055	−10·61	−10·49
99·8	0·2	0·0110	−10·31	−10·24
99·5	0·5	0·0282	− 9·90	− 9·91
99·0	1·0	0·0581	− 9·59	− 9·61
98·0	2·0	0·125	− 9·25	− 9·26
96·0	4·0	0·293	− 8·88	− 8·89
95·0	5·0	0·402	(− 8·75)	(−8·75)
94·0	6·0	0·532	− 8·62	− 8·63
92·0	8·0	0·897	− 8·40	− 8·40
90·0	10·0	1·53	− 8·18	− 8·19
87·5	12·5	3·48	− 7·81	− 7·91

* Hammett and others (*loc. cit.*): the calculation uses the experimental value for the acidity function of 95% sulphuric acid.

The Acidity Function of Oleum.—Values of the acidity function of fuming sulphuric acid containing between 0% and 14% of free sulphur trioxide (*i.e.*, sulphur trioxide in excess of the composition H_2SO_4) are collected in Table V.

TABLE V.

Acidity function of fuming sulphuric acid.

SO_3, %	0·0	2·0	4·0	6·0	8·0	10·0	12·0	14·0
H_2SO_4, %	100·0	100·45	100·90	101·35	101·80	102·25	102·70	103·15
$-H_0$	10·89	11·65	11·89	12·06	12·22	12·37	12·53	12·68

Equations (5) and (6) represent alternative possibilities for the equilibrium between the indicator and the medium, the former being analogous to the equilibrium (2):

$$ArNO_2 + H_2S_2O_7 \rightleftharpoons ArNO_2H^+ + S_2O_7H^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$ArNO_2 + SO_3 \rightleftharpoons ArNO_2{\cdot}SO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The ultra-violet spectra do not distinguish between the equilibria (5) and (6), but the question can be decided from the influence of bisulphate ions, added initially to the medium, on the

position of the indicator equilibrium. The addition of bisulphate ions establishes a further equilibrium, the position of which lies essentially on the right hand side of equation (7):

$$SO_4H^- + H_2S_2O_7 \rightleftharpoons H_2SO_4 + S_2O_7H^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Bisulphate ions, therefore, displace the indicator equilibrium (5) or (6) towards the left by the removal of pyrosulphuric acid (or "free" sulphur trioxide) by the reaction (7). If the indicator is engaged in the equilibrium (5) its ionisation will also be reduced by the mass-action effect of the $S_2O_7H^-$ ions produced in (7), but, on the other hand, if the equilibrium (6) is established, the indicator ionisation ratio will be comparatively insensitive to the presence of $S_2O_7H^-$ ions. The point can be tested by comparing the effects produced on the ionisation ratio of a suitable base by the addition of an equal molal concentration of water and of bisulphate ions. Water reacts quantitatively according to the equation $H_2O + H_2S_2O_7 = 2H_2SO_4$; bisulphate ions also remove pyrosulphuric acid, forming $S_2O_7H^-$ ions according to equation (7). If the indicator is involved in the equilibrium (6), the influences of water and of bisulphate ions on the indicator ionisation ratio should be similar, but if (5) is correct the effect of the bisulphate ions should exceed that of water.

The necessary comparison can be made from the results in Tables I and II, and the figures below show that the influence of potassium bisulphate on the ionisation ratio of *p*-chloronitrobenzene so far exceeds that of water as to leave no doubt that the mass-action effect of the $S_2O_7H^-$ ions on the indicator equilibrium is real. The equilibrium (5) is, therefore, established in the media under discussion, although the possibility remains that (6) may operate in very strong oleum.

Influence of water and potassium hydrogen sulphate on the ionisation ratio of p*-chloronitrobenzene* (medium: 103·55% H_2SO_4).

Added substance.		Concn., mol./kg.	log [B]/[BH⁺].	Added substance.		Concn., mol./kg.	log [B]/[BH⁺].
$KHSO_4$	.....	0·00	−1·35	H_2O	.....	0·00	−1·25
,,	.....	0·10	−1·01	,,	.....	0·10	−1·26
,,	.....	0·25	−0·67	,,	.....	0·25	−1·14
,,	.....	0·49	−0·25	,,	.....	0·49	−0·93
,,	.....	0·61	−0·07	,,	.....	0·61	−0·88

Some measurements of the degree of ionisation of 4:5-dibromo-2:7-dinitrofluorescein in weak oleum have been reported by Lewis and Bigeleisen (*loc. cit.*), but this compound is a cation base in such media and the related acidity function is H_+ and not H_0. These authors assumed that the equilibrium (6) was established between the indicator and the medium in all fuming acids, and calculated the acidity function of oleum from the partial vapour pressure of sulphur trioxide by the equation: H = a constant + log p_{SO_3}. The results (cf. Deane, *J. Amer. Chem. Soc.*, 1945, **67**, 329) are quite different from those reported in this paper. It has been claimed (Deane, *loc. cit.*) that the values obtained by Lewis and Bigeleisen are consistent with measurements of the rate of cyclisation of *o*-benzoylbenzoic acid, but the test is inconclusive because the acid does not ionise as a simple base in sulphuric acid solution (Newman, Knivila, and Garrett, *J. Amer. Chem. Soc.*, 1945, **67**, 704).

University of London, King's College, Strand, London, W.C.2.
The University, Glasgow, W.2.
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207. *Aromatic Sulphonation. Part II. Kinetics of Sulphonation in Fuming Sulphuric Acid.*

By J. C. D. Brand.

The kinetics of sulphonation of *p*-tolyltrimethylammonium methyl sulphate, phenyltrimethylammonium methyl sulphate, *p*-nitrotoluene, and nitrobenzene have been measured between 0° and 45° in oleum containing up to 33% of sulphur trioxide. The effect of varying initial concentrations and the retarding influence of potassium sulphate, barium sulphate, and barium di(methyl sulphate) have been studied. The experiments were conducted with an excess of sulphur trioxide and were of the first order with respect to the concentration of organic reactant, $-d[ArH]/dt = k_1[ArH]$. *p*-Nitrotoluene and nitrobenzene were present in the medium chiefly in a totally unreactive ionised form, and sulphonation occurred through the small equilibrium proportion of un-ionised base. For the quaternary ammonium methyl sulphates and for un-ionised *p*-nitrotoluene and nitrobenzene the variation of k_1 with the composition of the medium is expressed by the equation $\log k_1 = \log A + 2{\cdot}3 \log R$, where A is a parameter characteristic of the substance undergoing suphation and R is the stoicheiometric molar ratio $H_2S_2O_7 : H_2SO_4$. The constants of the Arrhenius equation have been evaluated.

The kinetics are shown to be consistent with the assumption that the governing step in sulphonation is: $SO_3H^+ + ArH = Ar{\cdot}SO_3H + H^+$. Relative values of the velocity coefficient of this reaction have been determined.

With emphasis on the theory of reaction kinetics, Hinshelwood and his collaborators (*J.*, **1939**, **1372**; **1944**, **469**, **649**; **1948**, **1065**) have studied the kinetics of sulphonation of several aromatic compounds by solutions in nitrobenzene of both sulphuric acid and sulphur trioxide. In this solvent the velocity of sulphonation by sulphur trioxide was of the second order with respect to sulphur trioxide and the reaction was retarded by the product; this was shown to be accounted for if the governing step involved S_2O_6 molecules:

$$2SO_3 \rightleftharpoons S_2O_6;\ S_2O_6 + ArH = ArS_2O_6H;\ ArS_2O_6H \rightleftharpoons ArSO_3H + SO_3.$$

The kinetics of sulphonation by sulphuric acid in nitrobenzene were consistent with a reversible mechanism involving attack by SO_3H^+ ions and represented by the equilibria

$$2H_2SO_4 \rightleftharpoons SO_3H^+ + SO_4H^- + H_2O$$
$$PhNO_2 + ArH + SO_3H^+ \rightleftharpoons PhNO_2H^+ + ArSO_3H$$

Sulphonation in Fuming Sulphuric Acid.—Little attention has been paid to the quantitative side of this reaction. The kinetics are quite different from those encountered with nitrobenzene as a solvent: the reaction is more vigorous and is usually not reversible, in the sense that the forward and reverse reactions do not occur under the same conditions. Lauer and others (*J. pr. Chem.*, **1935**, **144**, **32**; *Ber.*, **1936**, **69**, **2618**; **1937**, **70**, **333**) investigated the sulphonation of anthraquinone in oleum but, by varying the concentrations of both reactants simultaneously, obtained a very complicated result which will be discussed later (§ 3). Lauer concluded that molecular (undissociated) sulphuric acid acted as the sulphonating agent both in concentrated and in fuming media, and that sulphur trioxide facilitated the reaction only through its ability to combine with the eliminated water molecule. The kinetics of sulphonation of *p*-nitrotoluene were examined by Martinsen (*Z. physikal. Chem.*, **1908**, **62**, **713**) in oleum containing 2·4% of sulphur trioxide and by Cowdrey and Davies (*J.*, **1949**, **1871**) in media containing 1—5·5% of sulphur trioxide. Martinsen also experimented in anhydrous sulphuric acid, and both authors made measurements in acids containing a small proportion of water. In weak oleum, Cowdrey and Davies found that the rate of reaction was given by the differential equation:

$$-d[C_7H_7{\cdot}NO_2]/dt = k_2[C_7H_7{\cdot}NO_2][SO_3] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $[SO_3]$ represents the stoicheiometric concentration of free sulphur trioxide. Martinsen's results also conform to equation (1) (Joffe, *J. Gen. Chem. Russia*, **1933**, **3**, **437**, **505**; *Abstr.*, **1934**, **178**) and a comparison of some of the published results with those reported in this paper is given in Table IV. However, because of a complicating ionisation of the *p*-nitrotoluene (Part I), these kinetics are not altogether typical of sulphonation. In the following discussion, the kinetics of the most general case will be presented in § 1, and the nature of the changes introduced when the organic reactant is involved in a simultaneous ionisation will be reviewed in §§ 2 and 3.

1. *Kinetics of Sulphonation of Phenyltrimethylammonium and* p-*Tolylmethylammonium Salts.*—In the kinetic experiments the quaternary ammonium salts were introduced as their methyl sulphates, and the progress of the reaction was followed by a modification of Martinsen's

method. The *p*-tolyltrimethylammonium ion reacted exclusively in the *m*-position with respect to the trimethylammonium group, but the phenyltrimethylammonium ion yielded approximately 78% of phenyltrimethylammonium 3-sulphonate, *m*-$Me_3N^+{\cdot}C_6H_4{\cdot}SO_3^-$, together with 22% of the *o*- and *p*-isomers (Brand and Rutherford, *Research*, 1949, **2**, 195). The details of the analysis of the products will be published shortly. Because the initial concentration of the quaternary ion was low, the concentration of sulphur trioxide did not change significantly during reaction and individual experiments obeyed equation (2):

$$-d[ArNMe_3^+]/dt = k_1[ArNMe_3^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The results of a typical experiment are given below.

Expt. 120.

Temp., 25°. Medium, 15·74% of SO_3.

$[SO_3]$ { initial: 1·968 mols./kg. final: 1·923 mols./kg. (calc.: 1·937 mols./kg.).

Time, mins.	Concn. of $PhNMe_3^+$ SO_4Me^-, mol./kg.	Total reaction, %.	10^3k_1, $min.^{-1}$.	Time, mins.	Concn. of $PhNMe_3^+$ SO_4Me^-, mol./kg.	Total reaction, %.	10^3k_1, $min.^{-1}$.
0·0	0·0312	0	—	13·6	0·0177	43·5	41·6
2·8	0·0280	10·4	39·5	18·7	0·0144	53·9	41·5
5·7	0·0247	20·9	41·2	24·6	0·0112	64·1	41·6
9·6	0·0211	32·5	40·8				

$41·0 \pm 0·6$

The results of all velocity measurements are collected in Tables I—VII. Concentrations are expressed in moles per kg. of solution and the time is in minutes. For a given temperature the results may be summarised as follows.

(a) *Influence of composition of medium.* The rate of reaction is a function of the free sulphur trioxide concentration raised to a high and variable power. The reaction order with respect to the molar concentration rises from 2·7 in 4—8% oleum to 4·6 in 16—20% oleum, and a relation of the form $k_1 \propto [SO_3]^n$ applies only if n is expressed as a function of the composition of the medium. A satisfactory empirical correlation exists between k_1 and the molar ratio $H_2S_2O_7 : H_2SO_4$ of the form

$$\log k_1 = \log A + 2·3 \log([H_2S_2O_7]/[H_2SO_4]) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where A is a constant characteristic of the substance undergoing sulphonation (Fig. 1).* The ratio $H_2S_2O_7 : H_2SO_4$ will be written hereafter as R. R is calculated assuming (1) that bisulphate ions react quantitatively according to the equation $SO_3 + SO_4H^- = S_2O_7H^-$, and (2) that the remainder of the free sulphur trioxide is present as molecular pyrosulphuric acid, $H_2S_2O_7$. Methosulphate ($MeSO_4^-$) ions† are counted as bisulphate (SO_4H^-). Assumption (2) is a reasonable first approximation in the moderately dilute oleum under discussion, where the proportion of *molecular* sulphur trioxide is small (Miles, Niblock, and Wilson, *Trans. Faraday Soc.*, 1940, **36**, 345; Miles, Niblock, and Smith, *ibid.*, 1944, **40**, 281); moreover, equation (3) is, for the time being, used quite empirically. The experimental results are given in Table I; values of k_1 are in column 8.

(b) *Influence of basic substances and reactant concentration.* Most inorganic salts are basic towards oleum, and experiments were made to determine the kinetic influence of potassium sulphate, potassium hydrogen sulphate, and barium di(methyl sulphate). These salts retard sulphonation powerfully, and the measured velocities of reaction are given in Table II, column 10. The reaction was also retarded by increasing the concentration of quaternary ammonium ion, but, by simultaneously varying the concentrations of the latter and those of barium di(methyl sulphate) in such a way that the total concentration of methosulphate ions remained constant, it could be shown that the velocity coefficient was approximately independent of the concentration of quaternary ion although very sensitive to alterations in the concentration of methosulphate ions. Equation (2) was, however, essentially valid to cover variations of the initial concentration of quaternary ammonium ion. (This follows, for example, if experiments 97 and 98, Table II, are compared with experiments

* Equations (3), (5), (7), (8), and (9) were empirically satisfactory in oleum containing 1—35% of sulphur trioxide, but are meaningless if extrapolated to 100% sulphuric acid ($R = 0$) or to very strong oleum.

† Salts containing the grouping $\geq\overset{+}{N}Me(MeSO_4^-)$ are commonly termed "methosulphates," *e.g.*, pyridine methosulphate. The convenient wording "methosulphate ion" is, however, used to denote $MeSO_4^-$, as this is unlikely to cause confusion. Ed.

TABLE I.

Influence of medium on the rate of sulphonation (temp. 25°).

Medium.								
Sulphur trioxide.								
Acid no.	%	mol./kg.	log R.	H_0.	Expt. no.	Initial concn. of $C_7H_7{\cdot}NMe_2{\cdot}SO_4Me$.	10^5k_1, min.$^{-1}$.	$H_0 + \log 10^5k_1 - \log R$.
13	2·44	0·305	−1·54	−11·52	87	0·0330	85	−8·05
13	2·44	0·305	−1·54	—	84	0·0300	86	−8·05
13	2·44	0·305	−1·54	—	83	0·0283	86	−8·05
18	4·10	0·513	−1·28	−11·81	155	0·0308	302	−8·05
18	4·11	0·514	−1·28	—	158	0·0302	303	−8·05
12	7·92	0·990	−0·94	−12·14	82	0·0316	1500	−8·02
12	7·92	0·990	−0·94	—	81	0·0273	1800	−7·94
12	7·94	0·992	−0·94	—	80	0·0252	1800	−7·94
11	11·50	1·439	−0·74	−12·27	78	0·0888	5400	−7·80
						$PhNMe_2SO_4Me$.		
18	4·08	0·510	−1·28	−11·81	167	0·0301	0·741	−10·66
18	4·10	0·513	−1·28	—	156	0·0304	0·748	−10·66
17	8·23	1·03	−0·92	−12·17	152	0·0301	4·80	−10·57
17	8·23	1·03	−0·92	—	154	0·0300	4·81	−10·57
11	11·60	1·451	−0·72	−12·42	105	0·0296	13·7	−10·56
11	11·60	1·451	−0·72	—	107	0·0302	13·6	−10·57
6	13·04	1·63	−0·66	−12·32	50	0·1036	12·4	−10·57
15	13·39	1·674	−0·64	−12·55	140	0·0304	22·1	−10·57
15	13·40	1·675	−0·64	—	141	0·0299	22·7	−10·55
14	15·74	1·968	−0·53	−12·73	120	0·0312	41·8	−10·58
14	15·74	1·968	−0·53	—	122	0·0297	42·2	−10·57
16	20·12	2·515	−0·35	−13·04	146	0·0300	129	−10·58
16	20·12	2·515	−0·35	—	143	0·0303	127	−10·59
10	24·2	3·02	−0·20	—	73	0·112	240	—
10	24·2	3·02	−0·20	—	74	0·0974	240	—
10	24·2	3·02	−0·20	—	75	0·106	230	—
5	33·1	4·13	+0·20	—	72	0·0964	2000	—

$C_7H_7{\cdot}NMe_2^+$: $\log k_1 = 2{\cdot}3_3 + 2{\cdot}2_4 \log R$. $PhNMe_2^+$: $\log k_1 = -0{\cdot}12 + 2{\cdot}3_4 \log R$.

84, Table I, or 99 and 104 with 101.) Potassium sulphate and barium di(methyl sulphate) exerted roughly the same kinetic effect at the same molar concentration, and the small difference which was observed was probably due to the methyl hydrogen sulphate released in solution from the latter, because the retardation produced by potassium and barium sulphates was indistinguishable (Table VI).

Qualitatively, the retardation by bases is readily interpreted. The effect is caused by the bisulphate ions into which both sulphate and methosulphate ions are converted by the reactions $SO_4^{--} + H_2SO_4 = 2SO_4H^-$ and $SO_4Me^- + H_2SO_4 = MeSO_4H + SO_4H^-$ respectively. The bisulphate ions and molecular pyrosulphuric acid establish the equilibrium

$$SO_4H^- + H_2S_2O_7 = S_2O_7H^- + H_2SO_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

the position of which lies on the right hand side (Brand, *J.*, 1946, 880). The consumption of pyrosulphuric acid according to equation (4) will diminish the rate of sulphonation, but this effect alone is insufficient to account for the observed retardation, even on the assumption that reaction (4) proceeds quantitatively from left to right. This is illustrated, for example, by the fact that the retardation produced by bisulphate ions is more than twice as great as that brought about by the same number of moles of water. [More exactly, the comparison is between the number of moles of potassium hydrogen sulphate (n_1) and of water (n_2) which produce the same change in R, but n_1 and n_2 are approximately equal.] The difference is not a primary salt effect, because no change occurs if the potassium ions are replaced by barium ions, and it is assumed to arise from a mass-action effect of the hydrogen pyrosulphate anions on the equilibria which determine the concentration of the sulphonating agent. The empirical equation (3) does not hold in the presence of added bisulphate ions, unless an additional term is included.

2. *Kinetics of Sulphonation of* p-*Nitrotoluene.*—The velocity of sulphonation of *p*-nitrotoluene was measured by the method referred to in § 1. The experiments yielded first-order rate coefficients (equation 2*a*), except in a limited number of cases in which the concentrations of sulphur trioxide and *p*-nitrotoluene were commensurate and equation (1) was obeyed (Table IV).

$$-[dArNO_2]/dt = k_1[ArNO_2] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a$$

TABLE II.

Influence of basic substances and reactant concentration (temp., 25°).

Medium. Sulphur trioxide. Acid no.	%	mol./kg.	log R.	H_0 *	Expt. no.	Initial concn. of p-C_7H_7·NMe_2SO_4Me.	Added substance.	equiv./kg.	10^5k_1.	$H_0 + \log 10^5k_1 - \log R$.
13	2·46	0·307	−1·52	−11·59	86	0·0151	—	—	109	−8·03
		0·307	−1·52	−11·59	85	0·0156	—	—	109	−8·03
		0·305	−1·54	−11·52	Table I	0·030	—	—	86	−8·05
		0·290	−1·64	−11·34	101	0·0744	—	—	49	−8·01
		0·292	−1·66	−11·32	104	0·0304	K_2SO_4	0·0509	47	−7·99
		0·291	−1·75	−11·15	102	0·0300	K_2SO_4	0·0903	30	−7·92
	2·31	0·289	—	—	103	0·0297	K_2SO_4	0·179	15	—
		0·302	−1·55	−11·52	97	0·0150	$Ba(SO_4Me)_2$	0·0147	91	−8·01
		0·300	−1·55	−11·51	98	0·0152	$Ba(SO_4Me)_2$	0·0161	89	−8·01
		0·295	−1·65	−11·33	99	0·0294	$Ba(SO_4Me)_2$	0·0509	55	−7·94
		0·291	−1·77	−11·11	100	0·0286	$Ba(SO_4Me)_2$	0·1007	32	−7·84
						$PhNMe_2SO_4Me$.				
11	11·60	1·45	−0·72	−12·41	Table I	0·0300	—	—	13·6	−10·55
		1·43	−0·72	−12·31	109	0·0733	—	—	10·0	−10·57
		1·43	−0·74	−12·31	110	0·0747	—	—	10·0	−10·57
		1·44	−0·74	−12·30	111	0·0296	$Ba(SO_4Me)_2$	0·0503	10·8	−10·53
		1·44	−0·74	−12·30	108	0·0292	$Ba(SO_4Me)_2$	0·0496	11·3	−10·51
		1·38	—	—	119	0·0297	$Ba(SO_4Me)_2$	0·248	4·58	—
		1·44	−0·74	−12·30	112	0·0295	K_2SO_4	0·0501	10·2	−10·55
		1·43	−0·75	−12·20	117	0·0303	K_2SO_4	0·0870	8·19	−10·54
		1·43	−0·78	−12·04	116	0·0303	K_2SO_4	0·150	5·85	−10·49
	11·28	1·41	−0·82	−11·80	118	0·0300	K_2SO_4	0·250	3·66	−10·42
14	15·64	1·968	−0·53	−12·73	Table I	0·030	—	—	42·0	−10·57
		1·934	−0·56	−12·43	128	0·0292	$Ba(SO_4Me)_2$	0·100	27·6	−10·43
		1·951	−0·56	−12·43	131	0·0303	K_2SO_4	0·098	25·4	−10·47
		1·925	−0·60	−12·14	135	0·0299	K_2SO_4	0·250	12·1	−10·46
	14·97	1·871	−0·69	−11·69	137	0·0303	K_2SO_4	0·501	4·40	(−10·36)
		1·844	−0·75	—	139	0·0302	K_2SO_4	0·649	2·47	—
		1·942	−0·56	−12·43	134	0·0305	$KHSO_4$	0·100	25·1	−10·47
		1·942	−0·56	−12·43	132	0·0301	$KHSO_4$	0·100	24·5	−10·48
16	20·12	2·515	−0·35	−13·04	Table I	0·0301	—	—	128	−10·58
		2·49	−0·37	−12·75	148	0·0305	K_2SO_4	0·0101	77·0	−10·49
		2·46	−0·41	−12·40	149	0·0302	K_2SO_4	0·246	39·0	−10·40
	19·20	2·40	−0·48	−11·95	151	0·0305	K_2SO_4	0·498	14·2	(−10·32)

* Part I.

(a) *Influence of medium composition.* The variation of the coefficient k_ψ with the strength of the medium is shown in Table III, column 8. In weak oleum the order of the reaction with

TABLE III.

Influence of medium on the rate of sulphonation of p*-nitrotoluene* ($pK_a = -10{\cdot}28$).

Medium.						Initial concn. of p-$C_7H_7{\cdot}NO_2$, mol./kg.	10^5k_ψ, min.$^{-1}$.	$pK_a + \log 10^5k_\psi - \log R$.
Acid no.	Sulphur trioxide. %	Sulphur trioxide. mol./kg.	log R.	Expt. no.	Temp.			
3	0·75	0·094	−2·17	21	35°	0·0257	2·20	−7·77
3	0·78	0·097	−2·16	20	—	0·0282	2·15	−7·79
1	2·13	0·267	−1·60	10	—	0·0241	7·27	−7·82
1	—	0·270	−1·60	7	—	0·0247	7·18	−7·82
2	7·37	0·921	−0·97	28	—	0·0246	36·5	−7·75
2	—	0·923	−0·97	15	—	0·0242	37·8	−7·73
2	—	0·923	−0·97	14	—	0·0264	37·0	−7·74
4	13·76	1·720	−0·62	32	—	0·0244	107	−7·63
4	—	1·720	−0·62	33	—	0·0248	103	−7·67
2	7·26	0·908	−1·02	22	—	0·1198	34·8	−7·72
2	—	0·911	−1·02	13	—	0·1205	34·3	−7·72
9	7·45	0·931	−1·01	61	—	0·1208	36·2	−7·71
9	—	0·931	−1·01	62	—	0·1216	36·0	−7·71
8	11·35	1·419	−0·76	63	—	0·1191	75·8	−7·64
4	—	1·696	−0·64	35	—	0·1248	102·6	−7·63
4	—	1·696	−0·64	36	—	0·1266	102·8	−7·63
4	—	1·698	−0·64	31	—	0·1203	103·1	−7·63
4	13·61	1·701	−0·64	30	—	0·1211	104·3	−7·62
18	4·11	0·514	−1·28	160	25°	0·0302	5·58	−8·25
18	—	0·516	−1·28	157	—	0·0302	5·50	−8·26
17	8·28	1·035	−0·92	153	—	0·0299	15·6	−8·17
15	13·38	1·672	−0·64	142	—	0·0307	33·4	−8·11
14	—	1·974	−0·53	127	—	0·0322	45·3	−8·09
14	15·8	1·975	−0·53	129	—	0·0296	45·2	−8·09
16	20·2	2·52	−0·35	144	—	0·0308	73	−8·07
16	—	2·52	−0·35	150	—	0·0301	73	−8·07
9	7·45	0·931	−1·01	60	—	0·1196	13·7	−8·13
8	11·35	1·419	−0·76	59	—	0·1163	26·2	−8·10
8	—	1·420	−0·76	58	—	0·1201	26·3	−8·10
11	—	1·437	−0·75	106	—	0·1189	26·0	−8·11
4	—	1·696	−0·64	39	—	0·1181	35·5	−8·09
4	13·6	1·699	−0·64	37	—	0·1180	35·7	−8·09

respect to the concentration of sulphur trioxide was close to unity (cf. Cowdrey and Davies, *loc. cit.*), but it failed to remain constant, becoming greater in stronger media (Table IV). The results were satisfactorily expressed by the equation :

$$\log k_\psi = -0{\cdot}74 + 1{\cdot}1_7 \log R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

which resembles equation (3) except that the order of reaction with respect to R is now $1{\cdot}1_7$ (Fig. 1). The reaction was much slower than might have been expected from the results in § 1. For example, in oleum containing 16% of sulphur trioxide, p-nitrotoluene reacted more slowly than the phenyltrimethylammonium ion although in the same medium the p-tolyltrimethylammonium ion reacted too rapidly for measurement. This lack of reactivity was associated with the ability of p-nitrotoluene to ionise as a base in sulphuric acid (equation 6) since the

$$C_7H_7{\cdot}NO_2 + H_2SO_4 \rightleftharpoons C_7H_7{\cdot}NO_2H^+ + SO_4H^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

ionised form would react less readily than the uncharged molecule with an electrophilic reagent. In oleum, the proportion of reactive, un-ionised base is quite small as shown by the figures below (10^{-4}—10^{-5}M-solution) :

SO_3, %	0	2	4	6	8	10	12	14	16
Un-ionised p-nitrotoluene, %	19·7	4·1	2·4	1·7	1·1	0·81	0·56	0·40	0·27

In solutions which are more concentrated with respect to p-nitrotoluene the proportion of the un-ionised form is somewhat greater. Assuming that the ion, $C_7H_7{\cdot}NO_2H^+$, is so unreactive that sulphonation occurs entirely through the small equilibrium proportion of

TABLE IV.

Second-order velocity coefficients of the sulphonation of p-*nitrotoluene* (*temp.* 25°).

Medium. Sulphur trioxide. %.	mol./l.	Expt. no.	Initial concn. of $C_7H_7{\cdot}NO_2$, mol./l.	10^3k_2 (min. mole/l.)$^{-1}$.	Ref
2·4	0·56	—	0·20	5·6	1
2·4	0·56	—	0·40	4·8	1
2·18	0·50	4	0·17	4·4	3
2·16	0·50	3	0·26	4·1	3
2·17	0·50	1	0·29	4·0	3
2·14	0·49	5	0·36	3·7	3
4·12	0·96	—	0·05	5·2	3
7·45	1·75	60	0·22	7·3	3
13·3	3·14	46	0·44	11·3	3
0·91	0·21	—	0·20	5·0	2
2·47	0·69	—	0·20	5·2	2
5·47	1·27	—	0·20	5·7	2

References: 1, Martinsen, *loc. cit.* 2, Cowdrey and Davies, *loc. cit.* 3, This paper.
N.B.—In this Table, concentrations are expressed in *moles per litre*.

un-ionised base, the true velocity of reaction, calculated on the concentration of *un-ionised* *p*-nitrotoluene, would be obtained by dividing the observed values of k_2 by the proportion of un-ionised molecules. When this is done (Table V and Fig. 1), the corrected coefficients, k_1, show (i) that the order of reaction with respect to R is 2·3, and (ii) that the absolute rate of reaction is similar to that observed for the *p*-tolyltrimethylammonium ion. The empirical equation which fits the results is

$$\log k_1 = 2{\cdot}32 + 2{\cdot}3_3 \log R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The kinetics of sulphonation of the quaternary ammonium ions and of *p*-nitrotoluene are compatible, therefore, if allowance is made for the basic ionisation of the latter.

TABLE V.

Velocity of sulphonation of un-ionised p-*nitrotoluene* (*temp.* 25°) ($pK_a = -10{\cdot}28$).

Medium. Sulphur trioxide. %.	mol./kg.	log R.	H_0.	Fraction of un-ionised $C_7H_7{\cdot}NO_2$.	log 10^3k_2.	log 10^3k_1
2·14	0·267	−1·56	−11·65	0·0464	0·41	1·74
4·12	0·515	−1·24	−11·89	0·0239	0·74	2·36
7·38	0·922	−0·966	−12·17	0·0127	1·11	3·01
8·24	1·03	−0·906	−12·25	0·0106	1·19	3·16
11·36	1·42	−0·730	−12·48	0·0063	1·42	3·62
13·36	1·67	−0·632	−12·63	0·0045	1·52	3·87
15·76	1·97	−0·527	−12·81	0·0029	1·66	4·19
20·16	2·52	−0·349	−13·12	0·0014	1·86	4·70

(b) *Influence of added bases.* The sulphonation of *p*-nitrotoluene is retarded by increasing the concentration of reactant and by adding potassium sulphate or other bases to the solution (Table VI). Potassium and barium sulphates produce the same retardation at the same molar concentration. The diminution in velocity brought about by increasing the concentration of *p*-nitrotoluene is accounted for by the basicity of the compound, since the same effect is produced by an equivalent of other bases (*e.g.*, experiments 165 and 166, Table VI). The retarding influence of potassium and barium sulphates on the rate of sulphonation is much smaller than was observed with the quaternary ammonium ions, and is accounted for quantitatively by the removal of free sulphur trioxide according to equation (4). This is illustrated by the entries in the final column of Table VI, where it is shown that ($\log k_1 - \log R$) is approximately constant. (The agreement would be improved by introducing the empirical order of 1·17 from equation 5.) The velocity of reaction is, therefore, a function of the medium composition only, and equation (5) is valid in the presence of bases.

The failure of the hydrogen pyrosulphate ions to retard the reaction is only apparent. It has been shown (Part I) that these ions would displace the equilibrium of *p*-nitrotoluene in favour of the un-ionised form and this effect, which of itself would increase the velocity of reaction, opposes the inherently retarding influence of the $S_2O_7H^-$ ions. The fact that these

effects so nearly balance one another is an important clue to the nature of the sulphonating agent, because it demonstrates that the concentrations of un-ionised *p*-nitrotoluene and substituting agent are affected proportionately, but in opposite senses, by a change in the acidity of the medium. With a small qualification, this is precisely the property possessed by two independent acid–base systems ($B_1H^+ \overset{K_1}{\rightleftharpoons} B_1 + H^+$; $B_2H^+ \overset{K_2}{\rightleftharpoons} B_2 + H^+$), it being readily shown that

$$[B_1][B_2H^+]/[B_1H^+][B_2] = K_1/K_2$$

(Square brackets refer to concentrations; the terms involving activity coefficients are symmetrical and have been disregarded.) The analogy with the sulphonation kinetics is demonstrated as follows: let $[B_1]$ represent the fraction of the total concentration of *p*-nitrotoluene present in the un-ionised form, let $[B_2H^+]$ represent the fractional concentration of the sulphonating agent similarly, and assume that the degree of conversion of B_2 into B_2H^+ is small. Then, because both $[B_1]$ and $[B_2H^+]$ are small compared with $[B_1H^+]$ and $[B_2]$ respectively, the rate of sulphonation, which is proportional to the product $[B_1][B_2H^+]$, is seen by rearrangement of the equation above to be constant if the *acidity* of the medium changes, *i.e.* if the total concentrations of $[B_1] + [B_1H^+]$ and $[B_2] + [B_2H^+]$ remain constant. This is the experimental result.

FIG. 1.

Variation of rate coefficients and acidity function with composition of the medium.

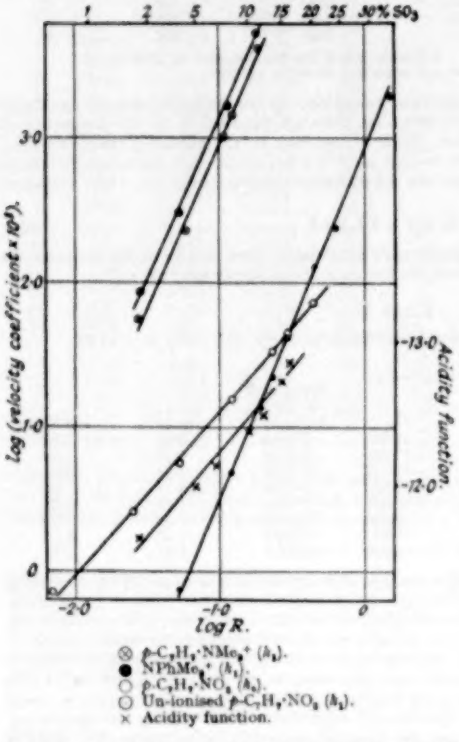

FIG. 2.

Variation of the velocity of sulphonation of nitrobenzene with the composition of the medium.

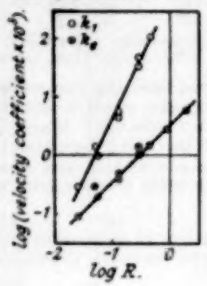

FIG. 3.

Variation of the partial pressure of sulphur trioxide with medium composition.

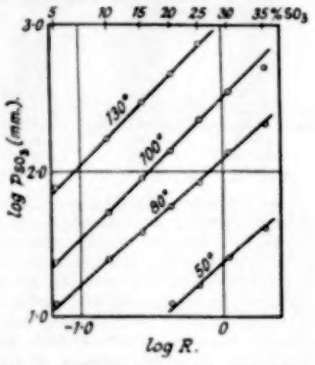

TABLE VI.

Influence of basic substances and reactant concentration upon the velocity of sulphonation of p-*nitrotoluene* (pK_a −10·28).

Medium.										
Sulphur trioxide.							Added substance.			
Acid no.	%.	mol./kg.	log *R*.	Temp.	Expt. no.	Initial concn. of *p*-$C_7H_7{\cdot}NO_2$.		equiv./kg.	10^5k_ψ min.$^{-1}$.	pK_a + log 10^5k_ψ − log *R*.
1	2·14	0·268	−1·60	35°	Table III	0·0244	—	—	7·23	−7·62
		0·269	−1·67	—	8	0·0614	—	—	7·0	−7·77
2	7·37	0·922	−0·98	—	Table III	0·025	—	—	37·1	−7·73
		0·915	−1·01	—	12	0·0873	—	—	34·0	−7·74
		0·910	−1·05	—	27	0·0251	K_2SO_4	0·130	32·0	−7·72
		0·898	−1·15	—	26	0·0256	K_2SO_4	0·281	26·0	−7·71
	7·28	0·910	−1·02	—	Table III	0·120	—	—	34·5	−7·72
		0·901	−1·09	—	23	0·119	K_2SO_4	0·098	31·2	−7·70
		0·900	−1·10	—	24	0·114	K_2SO_4	0·126	29·6	−7·71
		0·892	−1·17	—	23	0·119	K_2SO_4	0·217	26·3	−7·69
18	4·12	0·515	−1·28	25°	Table III	0·0304	—	—	5·54	−8·26
		0·508	−1·33	—	166	0·0790	—	—	5·20	−8·23
		0·508	−1·33	—	165	0·0306	$Ba(SO_4Me)_2$	0·0504	5·22	−8·23
4	13·6	1·697	−0·64	—	Table III	0·118	—	—	35·6	−8·08
		1·673	−0·68	—	47	0·120	K_2SO_4	0·1188	32·8	−8·08
		1·668	−0·71	—	40	0·117	K_2SO_4	0·1938	30·2	−8·09
		1·648	−0·76	—	41	0·117	K_2SO_4	0·3168	27·4	−8·09
		1·633	−0·79	—	44	0·117	K_2SO_4	0·3990	25·0	−8·09
		1·661	−0·70	—	42	0·128	$BaSO_4$	0·1644	31·9	−8·08
		1·644	−0·73	—	45	0·118	$BaSO_4$	0·2370	30·0	−8·08
		1·627	−0·77	—	43	0·117	$BaSO_4$	0·3516	25·5	−8·10
14	15·8	1·974	−0·53	—	Table III	0·031	—	—	45·2	−8·09
		1·947	−0·57	—	133	0·0304	K_2SO_4	0·158	41·7	−8·09
		1·921	−0·60	—	136	0·0302	K_2SO_4	0·253	38·0	−8·10
		1·878	−0·68	—	138	0·0308	K_2SO_4	0·498	31·1	−8·11

3. *Kinetics of Sulphonation of Nitrobenzene.*—The velocity of sulphonation of nitrobenzene was measured spectrometrically at 20°. The variation of the experimental coefficient, k_ψ, with the composition of the medium was similar to that described for *p*-nitrotoluene in § 2 (Fig. 2). The results are expressed by the empirical relation

$$\log k_\psi = -2{\cdot}4 + 1{\cdot}0 \log R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

The ionisation of nitrobenzene in oleum is extensive, although not so complete as that of *p*-nitrotoluene as the following figures illustrate:

SO_3, %	0	4	8	12	16
Percentage of un-ionised nitrobenzene	70	19	9·9	5·1	2·5

The velocity of sulphonation of un-ionised nitrobenzene can be obtained by the method of § 2a, and is given (Fig. 2) by

$$\log k_1 = -0{\cdot}2 + 2{\cdot}3_5 \log R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Comparing the reactivity of nitrobenzene ($k_{1(a)}$) and the phenyltrimethylammonium ion ($k_{1(b)}$), we obtain from Tables I and VII and equation (9), $k_{1(a)}/k_{1(b)} = 1{\cdot}3$ at 20°. In 87—97% sulphuric acid, where nitrobenzene is un-ionised, the relative rate of nitration is 1·9 at 25° (Bonner, James, Lowen, and Williams, *Nature*, 1949, **163**, 955).

TABLE VII.

Variation of temperature.

	Medium.					
		Sulphur trioxide.				
Temp.	Acid no.	%.	mol./kg.	Expt. no.	Initial concn. of p-$C_7H_7{\cdot}NMe_2SO_4Me$.	10^2k_1 min.$^{-1}$.
14·0°	13	2·44	0·305	91	0·0280	39
14·9	13	2·44	0·305	92	0·0293	41
14·9	13	2·43	0·304	93	0·0307	40
20·0	13	2·44	0·305	94	0·0259	64·3
20·0	13	2·43	0·304	95	0·0314	53·8
20·0	13	2·42	0·303	96	0·0303	62·8
35·0	13	2·44	0·305	88	0·0320	180
35·0	13	2·45	0·306	89	0·0301	210
35·0	13	2·44	0·305	90	0·0277	188
0·0	18	4·09	0·512	161	0·0301	38·9
0·0	18	4·11	0·514	159	0·0303	38·7
					$NPhMe_2$, SO_4Me.	
45·0°	18	4·09	0·512	164	0·0301	4·21
45·0	18	4·07	0·512	163	0·0302	4·26
0·0	11	11·60	1·450	113	0·0292	1·38
40·0	11	11·58	1·448	114	0·0301	45·2
40·0	11	11·61	1·451	115	0·0291	46·8
0·0	14	15·73	1·969	121	0·0290	4·24
0·0	14	15·72	1·968	124	0·0307	4·12
15·4	14	15·73	1·969	126	0·0302	18·4
40·0	14	15·73	1·969	123	0·0301	139·4
40·0	14	15·72	1·968	125	0·0302	140·4
0·0	16	20·1	2·515	147	0·0302	13·1
					p-$C_7H_7{\cdot}NO_2$.	10^2k_ψ.
45·0°	18	4·08	0·514	162	0·0306	44·7
15·0	9	7·45	0·931	66	0·120	4·38
45·0	9	7·45	0·931	65	0·119	115
15·0	8	11·35	1·42	67	0·120	5·81
45·0	8	11·35	1·42	64	0·119	147
0·0	14	15·75	1·97	130	0·0308	2·30
0·0	16	20·2	2·52	145	0·0300	3·82

Note on the Sulphonation of Anthraquinone.—The measurements of Lauer and others (*loc. cit.*) on the velocity of sulphonation of anthraquinone in oleum media were conducted with equal concentrations of anthraquinone and sulphur trioxide. First-order velocity coefficients were obtained which varied in a complicated fashion with reactant concentration. Dilute solutions of anthraquinone in oleum are almost quantitatively converted into the conjugate ion ($pK_a = -8{\cdot}15$), but the exceedingly concentrated solutions employed by Lauer contained a kinetically significant proportion of un-ionised anthraquinone, and the interpretation of

the results is not straightforward. The view of Lauer and his associates that undissociated sulphuric acid is the effective substituting agent in oleum depended on a mistaken process of correcting the experimental heat of activation by addition of the heat of solution of the product in different oleum media.

4. *Influence of Temperature.*—The variation of the velocity coefficients with temperature for several media may be seen from Table VII, together with results at 25° and 35° from previous tables. For a given medium, $\log k_1$ or $\log k_2$ is a linear function of $1/T$. The constants of the Arrhenius equation are assembled in Table VIII. The observation that the apparent heat of activation of *p*-nitrotoluene exceeds that of either of the quaternary ions is an independent argument for the existence of an unreactive form in solution, because in this case the temperature-dependent factor contains a term corresponding to the heat of the reaction represented by equation (10), reading from right to left:

$$p\text{-}C_7H_7\cdot NO_2 + H_2S_2O_7 \rightleftharpoons p\text{-}C_7H_7\cdot NO_2H^+ + S_2O_7H^- \quad . \quad . \quad . \quad . \quad . \quad (10)$$

The fact that the pre-exponential factor, A, is close to 10^{11} has been quoted elsewhere as evidence of a bimolecular reaction, but is misleading.

Within the error of measurement, the relative rate of sulphonation of the *p*-tolyl- and phenyl-trimethylammonium ions is accounted for by the difference in activation energies. The activation energies themselves are probably composite quantities.

TABLE VIII.

Constants of the equation, $k_1 = A.e^{-E/RT}$.*

Sulphur trioxide.		$NPhMe_3.SO_4Me$.		$p\text{-}C_7H_7\cdot NMe_3.SO_4Me$.		$p\text{-}C_7H_7\cdot NO_2$.	
%	concn. mol./kg.	E.	log A.	E.	log A.	E.†	log A.
2·13	0·267	—	—	—	—	19·9	10·23
2·44	0·305	—	—	13·5	7·07	—	—
4·10	0·513	16·3	7·05	13·2	7·42	19·6	10·32
7·45	0·931	—	—	—	—	19·7	10·75
11·35	1·42	—	—	—	—	19·5	10·91
11·60	1·45	14·9	7·30	—	—	—	—
13·7	1·71	—	—	—	—	19·4	10·99
15·7	1·97	15·0	7·82	—	—	19·3	11·06
20·1	2·52	14·9	8·27	—	—	19·2	11·18
24·2	3·02	15·2	8·72	—	—	—	—

* k_2 was used in the case of *p*-nitrotoluene: k_1 and k_2 were expressed in *seconds*$^{-1}$ at 25° for the calculation of the pre-exponential factor.

† Cowdrey and Davies (*loc. cit.*) found $E = 18$ kcals.

Discussion.

Interpretation of the kinetics is handicapped by incomplete knowledge of the equilibria prevailing in oleum, and by lack of information concerning the influence of the medium and other dielectric effects. It is possible, however, to account for the foregoing in a self-consistent way by assuming that the sulphonating agent in oleum is the ion SO_3H^+, and that substitution occurs according to the equation:

$$SO_3H^+ + ArH = ArSO_3H + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Stubbs, Williams, and Hinshelwood (*loc. cit.*) have previously assumed that the reactive ion SO_3H^+ is formed in solutions of sulphuric acid in nitrobenzene.

Variation of the Rate of Sulphonation with Composition of the Medium.—If the velocity coefficient of equation (11) is denoted by k, the equation for the rate of sulphonation takes the form

$$-d[ArH]/dt = k[ArH][SO_3H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Experimentally, equation (2) applies to a particular set of initial concentrations in a given medium. By combining it with equation (12) we obtain

$$\log k_1 = \log k + \log [SO_3H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

Equation (13) should describe the variation of k_1 with change of medium (apart from purely physical changes), change of reactant concentration, or any other condition except change of temperature. Assuming that *molecular* sulphur trioxide (SO_3) and the SO_3H^+ ion can be treated as a normal acid–base pair, their concentrations will be related to the acidity function

of the medium by equation (14), where K_A is the acidic ionisation constant of the ion SO_3H^+, a quantity of unknown magnitude:

$$H_0 = pK_A + \log [SO_3] - \log [SO_3H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

The concentration of molecular sulphur trioxide will be italicised to distinguish it from the stoicheiometric concentration of free sulphur trioxide. These quantities are not independent of one another (equilibrium 15), but are altogether different in magnitude.

The concentration of molecular sulphur trioxide is determined by the equilibrium (15), the equilibrium constant, K, of which, expressed in terms of concentrations, is given by $K = [H_2S_2O_7]/[H_2SO_4][SO_3]$.

$$H_2SO_4 + SO_3 \rightleftharpoons H_2S_2O_7 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

If the dissociation of pyrosulphuric acid, by equilibrium (15) or otherwise, is assumed to be small, the expression for the concentration of molecular sulphur trioxide becomes

$$\log [SO_3] = -\log K + \log R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

where R is the stoicheiometric molar ratio, $H_2S_2O_7/H_2SO_4$, defined in § 1a. Equation (16) may be tested by plotting $\log p_{(SO_3)}$ against $\log R$, where $p_{(SO_3)}$ is the partial pressure of sulphur trioxide in oleum (Fig. 3; data of Miles, Niblock, and Wilson, *loc. cit.*): the relation is linear up to 35% oleum, and the slope is unity at 100° and 0·9 at 50° (at lower temperatures the vapour pressure was insufficient for accurate measurement). This appears to justify the use of equation (16) and, by combination of it with (14), the expression for the concentration of the sulphonating agent becomes

$$\log [SO_3H^+] = (pK + pK_A) + \log R - H_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

Equation (17) can be used to evaluate the relative concentration of SO_3H^+ in different media, and the extent to which it is proportional to the velocity of sulphonation is illustrated in Table IX. Equation (17) may also be simplified by expressing the acidity function as an approximately linear function of $\log R$ (Fig. 1), $H_0 = -13{\cdot}5 - 1{\cdot}2 \log R$. Inserting this result into equation (17) gives: $\log [SO_3H^+] =$ a constant $+ 2{\cdot}2 \log R$, which is an expression of the same form as the empirical equations of § 1—3, and furnishes correctly the order of reaction with respect to R.

TABLE IX.

Relation between the velocity of sulphonation of $NPhMe_3^+$ *and the concentration of* SO_3H^+ *ions.*

(Initial concn. of $NPhMe_3.SO_4Me$: 0·03 mol./kg. Temp., 25°.)

Sulphur trioxide { %	4·09	8·23	11·60	13·4	15·7	20·1
Sulphur trioxide { concn., mol./kg.	0·51	1·03	1·45	1·67	1·97	2·51
Relative concn. of SO_3H^+	0·0069	0·0363	0·102	0·166	0·32	1·0
10^3k_1	0·75	4·8	13·6	22·4	42·0	128
$k_1/[SO_3H^+]$	0·11	0·13	0·13	0·13	0·13	0·13

The complete theoretical expression for the velocity of sulphonation of the quaternary ammonium ions and the un-ionised forms of *p*-nitrotoluene and nitrobenzene is obtained from equations (13) and (17), *viz.*:

$$\log k_1 = \log k + \log R - H_0 + (pK + pK_A) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

In the case of the nitro-compounds, the experimental coefficients, k_0, are related to the coefficients k_1 of the un-ionised forms by the equation, $k_0 = k_1[B]$, $[B]$ representing the fraction of the total concentration of the reactant present in the un-ionised form. In the regions where sulphonation occurs with measurable speed, both *p*-nitrotoluene and nitrobenzene are almost quantitatively ionised and, therefore, $\log [B] \sim pK_a - H_0$ (where pK_a is the acidic ionisation constant of the ionised form), and the expression for the observed velocity of sulphonation is (cf. Table X)

$$\log k_0 = \log k - \log R - pK_a + (pK + pK_A) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

Experimentally, the order of reaction with respect to R were observed to be 1·2 and 1·0 for *p*-nitrotoluene (equation 5) and nitrobenzene (equation 8) respectively. If attention is confined to a small range of composition of the medium, the variation of the sulphuric acid mole fraction may be neglected and, therefore, $[SO_3] \propto [SO_3]$ (cf. equation 16). Introducing this approximation in place of equation (16) yields $k_0 \propto [SO_3]$, which by combination with equation (2*a*) gives the empirical equation (1), which is a satisfactory expression in weak oleum over a limited range of medium composition.

TABLE X.

Dependence of the velocity of sulphonation of p-nitrotoluene on the concentration of molecular sulphur trioxide.

(Initial concn. of $C_7H_7{\cdot}NO_2$: 0·03 mol./kg. Temp., 25°.)

Sulphur trioxide {	%	0·75	4·11	8·28	13·4	15·8	20·2
	concn., mol./kg.	0·094	0·51	1·03	1·67	1·97	2·52
R		0·00676	0·0325	0·120	0·229	0·296	0·45
10^3k_1		0·75	5·58	15·6	33·4	45·3	73
k_1/R		0·11	0·11	0·13	0·15	0·15	0·16

The interpretation of the variation of the velocity of sulphonation with the composition of the medium may be summarised as follows: the substituting agent is assumed to be the ion SO_3H^+, the concentration of which is small compared with that of molecular sulphur trioxide; an increase in the total concentration of sulphur trioxide (all forms) brings about (i) an increase in the concentration of molecular sulphur trioxide, and (ii) an increase of acidity, producing a higher degree of conversion of molecular sulphur trioxide into SO_3H^+ ions. The factors (i) and (ii) co-operate, and contribute almost equally to the overall variation of k_1 with the medium composition. With *p*-nitrotoluene and nitrobenzene, (ii) is compensated by a proportionate diminution in the concentration of un-ionised forms, and the variation is accounted for by changes in the concentration of molecular sulphur trioxide alone.

The Influence of Added Salts.—A preliminary account of this subject was given in § 1*b* and § 2*b*, where it was shown that bisulphate ions retard the reaction (i) by diminishing the concentration of free sulphur trioxide according to equation (4), and (ii) by diminishing the acidity by production of $S_2O_7H^-$ ions; each of these factors lowers the concentration of SO_3H^+ ions (equation 14). For *p*-nitrotoluene and nitrobenzene, the changes in the concentration of the un-ionised forms of the nitro-compounds and in the concentration of SO_3H^+ ions are inversely proportional to one another, and the observed retardation is accounted for entirely by the first of the factors listed above. In the presence of salts giving rise initially to bisulphate ions, the extent to which the velocities of sulphonation of *p*-nitrotoluene and the phenyltrimethylammonium ion are proportional respectively to the concentrations of molecular sulphur trioxide and of SO_3H^+ ions is shown in Table XI.

TABLE XI.

Influence of bisulphate ions on the concentration of molecular sulphur trioxide and on the rate of sulphonation of p-nitrotoluene.

(Initial concn. of $C_7H_7{\cdot}NO_2$: 0·12 mol./kg. Temp., 25°.)

Medium.						
Sulphur trioxide.			Added substance.			
%	concn., mol./kg.	R.		concn., equiv./kg.	10^3k_1, min.$^{-1}$.	k_1/R
13·6	1·697	0·227	—	—	35·6	0·157
—	1·673	0·207	K_2SO_4	0·1188	32·8	0·158
—	1·661	0·200	$BaSO_4$	0·1644	31·9	0·159
—	1·668	0·196	K_2SO_4	0·1938	30·2	0·154
—	1·644	0·187	$BaSO_4$	0·2370	30·0	0·160
—	1·648	0·175	K_2SO_4	0·3168	27·4	0·156
13·0	1·627	0·169	$BaSO_4$	0·3516	25·5	0·151
—	1·633	0·161	K_2SO_4	0·3990	25·0	0·155

Influence of basic anions on the concentration of SO_3H^+ *and on the rate of sulphonation of* $NPhMe_3^+$ (temp., 25°).

Sulphur trioxide.		Added substance.		Initial concn. of $C_7H_7{\cdot}NO_2$,	Relative concn. of		
%	concn., mol./kg.		concn., equiv./kg.	mol./kg.	SO_3H^+.	10^3k_1.	$k_1/[SO_3H^+]$.
11·6	1·45	—	—	0·030*	1·0	13·6	0·0136
—	1·43	—	—	0·074	0·76	10·0	0·0132
—	1·44	K_2SO_4	0·0501	0·029	0·74	10·2	0·0137
—	1·44	$Ba(SO_4Me)_2$	0·0503	0·030	0·74	10·8	0·0145
—	1·43	K_2SO_4	0·0870	0·030	0·58	8·19	0·0141
11·4	1·43	K_2SO_4	0·150	0·039	0·37	5·8	0·0157

The equations (18) and (19) have been tested comprehensively by tabulating values of (log $k_1 + H_0$ − log R) and (log k_ψ + pK_a − log R) in the final colums of Tables I and II, and

Tables III and VI respectively. Each of these expressions is equal to (log k + a constant), and should, therefore, be constant for a particular aromatic compound at a fixed temperature, in so far as k is itself independent of the composition of the medium. Examination of the Tables shows that the extensive experimental variation of the rate of sulphonation is very largely accounted for by the theoretical equations (18) and (19). The deviations which are observed correspond to a gradual rise of k when the concentration of sulphur trioxide is increased, or in the presence of a large concentration of bisulphate ions. The average results obtained for the relative velocity of substitution according to equation (11) at 25° are:

	Relative velocity coefficient (eqn. 11).
p-$C_7H_7{\cdot}NMe_2SO_4Me$	360
Un-ionised p-$C_7H_7{\cdot}NO_2$	290
Un-ionised $PhNO_2$ *	1·5
$NPhMe_2SO_4Me$	1·0 (overall) 0·8 (*m*-positions)

* Calc. from results at 20°, using E = 22 kcals.

The sulphonation of unionised p-nitrotoluene occurred more slowly than that of the p-tolyltrimethylammonium ion, in spite of the fact that un-ionised nitrobenzene reacted faster than $NPhMe_3^+$. The difference is associated with the large interval between the basic strengths of p-nitrotoluene and nitrobenzene (Part I), the withdrawal of electrons from the aromatic nucleus by the nitro-group being quantitatively different in the two cases. The velocity of sulphonation of p-nitrotoluene was reduced, apparently, at least one-thousand-fold by the addition of a proton, and no definite kinetic evidence of reactivity on the part of the ionised form was obtained.

The scale of the relative velocities of sulphonation is more condensed than is observed for nitration of the same systems, even after taking account of the fact that the phenyltrimethylammonium ion is not sulphonated exclusively in the *m*-position; these two facts should, indeed, be considered together, for the SO_3H^+ ion, being less powerfully electrophilic, is less susceptible to electrostatic influences than is NO_2^+.

Experimental.

Materials.—Phenyltrimethylammonium methyl sulphate, m. p. 126°, and p-tolyltrimethylammonium methyl sulphate, m. p. 144·5°, were obtained from the corresponding tertiary amines and methyl sulphate in acetone. The purification of nitrobenzene and p-nitrotoluene was referred to in Part I. AnalaR Potassium sulphate, potassium hydrogen sulphate, and potassium nitrate were used and were dried before use. Pure barium sulphate was prepared by slowly adding 0·1M-barium hydroxide to very dilute (1%) boiling sulphuric acid. Barium di(methyl sulphate) [Found: Ba, 38·2, 38·4. Calc. for $Ba(SO_4Me)_2$: Ba, 38·2%)] was dried *in vacuo* over phosphoric oxide and used freshly prepared. The preparation and analysis of oleum have been described previously (Brand, *J.*, 1946, 585).

Velocity Measurements.—These were made at 15·0°, 20·0°, 25·0°, 35·0°, 40·0°, and 45·0° in a thermostatically controlled water-bath and at 0° in an ice-bath. The compound to undergo sulphonation was added as a solid to the oleum, and the start of the reaction timed from this addition. Tests made to determine whether thermal effects occurred on mixing showed a rise in temperature amounting in unfavourable cases to several tenths of a degree. Precautions were taken to compensate for this.

Sampling and Analysis.—For convenience, the solutions were prepared and analysed by weight. During the reaction, samples of the solution were removed by pipette and delivered into concentrated sulphuric acid containing sufficient water to react with the sulphur trioxide introduced. The method of analysis depended on the fact that the unsulphonated aromatic molecules were sufficiently reactive to be estimated quantitatively by nitration in the presence of the sulphonic acids (Martinsen, *loc. cit.*). This was accomplished by adding a standard solution of potassium nitrate in concentrated sulphuric acid to the "arrested" sample and, after a suitable interval, determining the nitric acid by pententiometric titration with ferrous sulphate (Treadwell and Vontobel, *Helv. Chim. Acta*, 1937, **20**, 573). The concentration of the reactant was calculated from the consumption of nitric acid.

The time required for quantitative nitration ranged from one minute or less for p-nitrotoluene to some 20 hours at 25° for phenyltrimethylammonium methyl sulphate. Tests showed that no nitration of p-nitrotoluene-*o*-sulphonic acid, p-tolyltrimethylammonium-2-sulphonate, 4 : 1 : 2-$Me_3N^+{\cdot}C_6H_3Me{\cdot}SO_3^-$, or phenyltrimethylammonium-3-sulphonate occurred in a corresponding period. The analysis was tested repeatedly; some typical results for p-nitrotoluene were:

Wt. taken, g.	0·1126	0·1304	0·0981	0·0677	0·0956	0·0907
Found, g.	0·1134	0·1302	0·0985	0·0668	0·0961	0·0906

(Total weight of 0·5951 g. estimated as 0·5956 g.)

Similar determinations with p-tolyltrimethylammonium methyl sulphate (M, 261) and phenyltrimethylammonium methyl sulphate (M, 247) gave an average molecular weight of 260 and 245, respectively.

Some decomposition occurred during the sulphonation of p-nitrotoluene, generating about 10^{-4} mole

of sulphur dioxide during complete reaction in the more concentrated media. Although the loss of *p*-nitrotoluene was, therefore, small, appreciable reduction of nitric acid occurred during the analysis by nitration, and a correction applied to allow for this raised the velocity coefficient by 1—2%.

Disappearance of Sulphur Trioxide during Sulphonation.—In a number of kinetic experiments the concentration of sulphur trioxide was determined at the end of reaction. Some typical results are given below for the sulphonation of phenyltrimethylammonium methyl sulphate, and indicate that the amount of moisture absorbed during manipulation is small. Similar results were obtained on using *p*-tolyltrimethylammonium methyl sulphate and *p*-nitrotoluene.

Expt. no.:	105	114	115	109	110	120	123
Initial concn. (M.) of $NPhMe_2SO_4Me$ ...	0·0296	0·0301	0·0291	0·0733	0·0747	0·0312	0·0301
Sulphur trioxide:							
Initial concn. (M.)	1·451	1·448	1·451	1·434	1·435	1·966	1·960
Final concn. { Found (M.)	1·405	1·391	1·432	1·359	1·360	1·923	1·934
Final concn. { Calc. (M.)	1·421	1·418	1·422	1·361	1·360	1·937	1·939
Final concn. { %	98·9	98·1	100·7	99·9	100·0	99·3	99·7

Measurement of the Velocity of Reaction by Alternative Methods.—(a) *Change in light absorption.* The velocity of sulphonation of nitrobenzene was obtained by measurement of the initial rate of change of the extinction coefficient, at λ 3650 A., of the solution in oleum. The initial concentration of nitrobenzene was approximately 10^{-4}M., and the results are shown in Fig. 2. As a test of the method, the velocity of sulphonation of *p*-nitrotoluene was also measured and compared with the value obtained by chemical analysis (Tables III and VII):

Temp.	Medium, $[SO_3]$, mol./kg.	k_1 (min.$^{-1}$). By light absorption.	By chem. analysis.
18°	0·513	0·00258	0·00251
—	0·280	0·00107	0·00106

(*b*) *Dilatometry.* Some experiments were made with a dilatometer so constructed that the capillary limb formed the stopper of the reaction vessel, but were discontinued. However the results served as a useful check and agreed with those obtained by chemical analysis:

Expt. no.	Temp.	Medium, $[SO_3]$, mol./kg.	Initial concn. of	mol./kg.	k_1 (min.$^{-1}$). By dilatometer.	By chem. analysis.
54	25°	1·437	*p*-$C_7H_7{\cdot}NO_2$	0·025	0·025	0·026
57	25	1·436	*p*-$C_7H_7{\cdot}NO_2$	0·026	0·025	0·026
53	25	1·62	*p*-$C_7H_7{\cdot}NO_2$	0·026	0·033	0·031
68	35	1·426	$NPhMe_2SO_4Me$	0·046	0·029	0·029 *

* The velocity coefficient is k_1 in this experiment.

(*c*) *Analysis of the sulphonic acid formed.* Experiments on the rate of formation of 4-nitrotoluene-2-sulphonic acid were carried out as follows. Samples of the reaction mixture were diluted with water, and the sulphuric acid was removed with barium carbonate; the resulting solution of barium 4-nitrotoluene-2-sulphonate (containing some barium carbonate) was concentrated to a standard volume and the barium determined gravimetrically by precipitation with sulphuric acid. The results of two such experiments were:

Expt. no.	Temp.	Medium, $[SO_3]$, mol./kg.	Initial concn. of *p*-$C_7H_7{\cdot}NO_2$, mol./kg.	k_1 (min.$^{-1}$) analysis for 4-nitrotoluene-2-sulphonic acid.	*p*-nitrotoluene.
70	25°	1·41	0·1212	0·026	0·026
71	25	1·41	0·1214	0·027	

King's College, London.
The University, Glasgow.

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NOTES.

The Chloro- and Iodo-acetates of Dihydrolanosterol and Dihydroagnosterol. By R. G. Curtis.

The *X*-ray examinations of derivatives containing atoms of high atomic weight have given considerable information concerning the arrangement of the rings and side chain in sterols (Crowfoot and Dunitz, *Nature*, 1948, **162**, 608). It is intended to apply this method of structure analysis to some of the wool-wax triterpenes, and for this purpose the iodoacetates of dihydrolanosterol and dihydroagnosterol have been prepared. They were obtained from the corresponding chloroacetates, potassium iodide, and acetone, the chloroacetates being readily prepared from chloroacetic anhydride and the alcohol. Attempts to esterify dihydrolanosterol and dihydroagnosterol with iodoacetyl chloride directly were not successful.

Experimental.—(a) *Dihydrolanosteryl chloroacetate* was prepared by heating dihydrolanosterol (5 g.) with chloroacetic anhydride (15 g.) on a steam-bath (3 hours); water was added, the mixture was warmed to destroy excess of anhydride, and the solid was washed with hot water and recrystallised three times

from hot chloroform (20 ml.)–methanol (60 ml.), to give fine white needles (3·6 g.), m. p. 114·5—115°, $[\alpha]_D^{20}$ +57·1° (*c*, 3 in chloroform) (Found: C, 76·2; H, 10·5. $C_{32}H_{51}O_4Cl$ requires C, 76·1; H, 10·6%).

(b) *Dihydroagnosteryl chloroacetate* prepared in like manner from dihydroagnosterol (5 g.) formed prisms (3·4 g.), m. p. 143·5—144°, $[\alpha]_D^{20}$ +89·3° (*c*, 3 in chloroform) (Found: C, 76·4; H, 10·0. $C_{32}H_{51}O_4Cl$ requires C, 76·4; H, 10·2%).

(c) *Dihydrolanosteryl iodoacetate* was prepared by refluxing (3 hours) the chloroacetate (1 g.) in acetone (50 ml.) with potassium iodide (3 g.). After removal of the solvent and thorough washing of the residue with water, three crystallisations from chloroform–methanol (1 : 3; 15 ml.) gave glistening prisms (0·65 g.), m. p. 105—105·5°, $[\alpha]_D^{20}$ +52·9° (*c*, 3 in chloroform) (Found: C, 64·6; H, 8·7; I, 21·3. $C_{32}H_{53}O_4I$ requires C, 64·6; H, 8·95; I, 21·3%).

Dihydrolanosterol, m. p. 142—143°, was obtained by hydrolysis of the iodoacetate with alcoholic potassium hydroxide (4%).

(d) *Dihydroagnosteryl iodoacetate* prepared in like manner from dihydroagnosteryl chloroacetate (1 g.) and thrice crystallised formed glistening plates (0·85 g.), m. p. 114—114·5°, $[\alpha]_D^{20}$ +67·5° (*c*, 3 in chloroform) (Found: C, 64·6; H, 8·6; I, 21·1. $C_{32}H_{53}O_4I$ requires C, 64·6; H, 8·6; I, 21·3%). Dihydroagnosterol, m. p. 154—155°, was obtained by hydrolysis of the iodoacetate with alcoholic potassium hydroxide (4%).

The dihydrolanosterol, m. p. 146—147°, $[\alpha]_D$ +62·8° (*c*, 3 in chloroform), and dihydroagnosterol, m. p. 158—159°, $[\alpha]_D$ +67·5° (*c*, 3 in chloroform), used were prepared according to the methods described by F. J. McGhie ("Contributions to the Chemistry of the Sterols," Thesis, London, 1947).

The author is indebted to H. L. Oates and L. Llewelyn of this laboratory for the microanalyses. This work forms part of the research programme of this Division.—Division of Industrial Chemistry, Commonwealth Scientific and Industrial Research Organisation, Australia. [*Received, December 14th*, 1949.]

The Nitration of pp'-Dichloroazobenzene. By C. D. Houghton and William A. Waters.

Previous workers (cf. Burns, McCombie, and Scarborough, *J.*, 1928, 2928) have established that azobenzene and many of its derivatives nitrate and brominate in the *para*-position to the azo-group. Further, the nitrations of both the *o*- and the *m*-methylazobenzenes in the 4- and 4'-positions and the bromination of *m*-methylazobenzene in the 4-position indicate that the azo-group (or possibly the phenylazo taken as a whole) has a greater orienting power than the methyl group. In connection with another investigation (see Ford, Waters, and Young, *J.*, 1950, 833) it was of interest to determine, from the mode of cationoid substitution of *pp'*-dichloroazobenzene, the relative orienting powers of the chloro- and azo-groups, and consequently both the nitration and the bromination of *pp'*-dichloroazobenzene have been examined.

The nitration of *pp'*-dichloroazobenzene with fuming nitric acid in glacial acetic acid solution yields a dichloronitroazoxybenzene, m. p. 134°, which can also be obtained by the direct nitration of *pp'*-dichloroazoxybenzene. Under less drastic conditions nitration of the azo-compound does not occur. The product, m. p. 134°, has previously been obtained from *pp'*-dichloroazoxybenzene by both Calm and Heumann (*Ber.*, 1880, **13**, 1184) and Heumann (*Ber.*, 1872, **5**, 912), but these early investigators did not attempt to determine its exact structure. Calm and Heumann showed that their azoxy-compound could be reduced with cold alcoholic ammonium sulphide to a 4 : 4'-dichloro-nitroazobenzene. We have repeated this work, and have now found that this nitro-compound, on further reduction with tin and hydrochloric acid, yields a mixture of amines from which, by condensation with phenanthraquinone, we have been able to isolate 6-chloro-1 : 2-3 : 4-dibenzphenazine, identical with the product prepared by Ullmann and Mauthner (*Ber.*, 1904, **36**, 4028) from 4-chloro-*o*-phenylenediamine.

The nitration of *pp'*-dichloroazobenzene therefore yields 4 : 4'-dichloro-2-nitroazoxybenzene. Whether the nitration of the azo-compound precedes its oxidation, or the reverse, is as yet undecided, but it is now clear that both the azo- and the azoxy-group have a very marked *ortho-para* orienting power.

We failed to achieve the direct bromination of *pp'*-dichloroazobenzene, but prepared a sample of 4 : 4'-*dichloro-2-bromoazobenzene* for reference purposes.

Experimental.—*pp'*-Dichloroazobenzene was prepared by condensing *p*-chloronitrosobenzene with *p*-chloroaniline, whilst *pp'*-dichloroazoxybenzene was obtained as a by-product of the preparation of *p*-chloronitrosobenzene.

4 : 4'-*Dichloro-2-nitroazoxybenzene* was obtained by dissolving *pp'*-dichloroazobenzene (3 g.) in a mixture of fuming nitric acid (50 ml.) and glacial acetic acid (20 ml.) at −10°. The mixture was poured into water after keeping it at 0° for 30 minutes, and the solid was collected and crystallised repeatedly from alcohol. It formed fine yellow needles, m. p. 134° (Found: C, 46·6; H, 2·2; N, 13·4. $C_{12}H_7O_3N_3Cl_2$ requires C, 46·5; H, 2·2; N, 13·4%). The same product was obtained by dissolving *pp'*-dichloroazoxybenzene in a similar mixture of nitric and acetic acids.

4 : 4'-*Dichloro-2-nitroazobenzene* was prepared by keeping the nitro-azoxy-compound overnight with a mixture of equal volumes of ethyl alcohol and saturated ammonium sulphide solution. The product was precipitated with water, collected, and freed from sulphur by crystallisation from alcohol. It formed deep orange-red needles, m. p. 210° (Found: C, 48·9; H, 2·35; N, 14·2. $C_{12}H_7O_2N_3Cl_2$ requires C, 49·0; H, 2·4; N, 14·2%). An attempt to synthesise this compound by condensing together *p*-chloronitrosobenzene and 4-chloro-2-nitroaniline failed; the nitro-amine could be recovered unchanged after the two substances had been heated under reflux in glacial acetic acid.

4 : 4'-Dichloro-2-nitroazobenzene (5 g.) was reduced by boiling it with granulated tin (5 g.) in alcohol under reflux, and adding, from time to time, small portions (2—3 ml.) of concentrated hydrochloric acid until most of the tin had dissolved. The solution was then filtered from tin, diluted with one quarter of its volume of water, boiled for ½ hour (charcoal), and refiltered. This filtrate was then heated for 10 minutes with an aqueous solution of phenanthraquinone (3·6 g.), sodium acetate (5 g.), and sodium

hydrogen sulphite (5 g.). 6-Chloro-1 : 2-3 : 4-dibenzphenazine gradually separated in filterable form. After crystallisation three times from nitrobenzene–glacial acetic acid (equal volumes) it formed pale yellow-green needles, m. p. 245°, which on sublimation in a vacuum gave white, feathery crystals, m. p. 246° (Found : C, 76·4; N, 8·8; Cl, 11·2. Calc. for $C_{16}H_{11}N_2Cl$: C, 76·4; N, 8·9; Cl, 11·3%). Ullmann and Mauthner (*loc. cit.*) describe this compound as forming pale yellow-green needles, m. p. 240°.

4 : 4'-*Dichloro-2-bromoazobenzene* was obtained by heating 4-chloro-2-bromoaniline (1·2 g.) with *p*-chloronitrosobenzene (0·8 g.) in glacial acetic acid at 100° for 10 minutes. The product crystallised from alcohol in orange-red needles, m. p. 145° (Found : C, 44·0; H, 2·1; N, 8·4. $C_{12}H_7N_2Cl_2Br$ requires C, 43·9; H, 2·2; N, 8·5%).

pp'-Dichloroazobenzene resisted bromination (i) by refluxing with bromine in glacial acetic acid solution in the presence of anhydrous sodium acetate, (ii) by heating for 10 hours at 100° with liquid bromine and a few drops of pyridine, and (iii) by heating at 100° in 90% sulphuric acid in the presence of both bromine and silver sulphate (compare Derbyshire and Waters, *J.*, 1950, 573).—The Dyson Perrins Laboratory, Oxford. [*Received, December 15th*, 1949.]

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p-Cymene-2-sulphonamides. By (Miss) S. M. Brown and G. H. Thomson.

During the investigation of new surface-active agents, it was found that some amine derivatives of *p*-cymene-2-sulphonyl chloride are more difficult to prepare than the corresponding derivatives from benzene- and toluene-sulphonyl chlorides.

All b. p.s and m. p.s are uncorrected.

Preparation of Pure p-Cymene.—Commercial *p*-cymene (1 kg.) was shaken three times with concentrated sulphuric acid (900 c.c. in all); the top layer was washed successively with water, 1% potassium permanganate solution, 2N-potasium carbonate solution, and water again, dried (Na_2SO_4), and distilled; b. p. 175—176°; yield, 510 g.

p-Cymene-2-sulphonyl Chloride.—*p*-Cymene (67 g.) at 0° was added dropwise to stirred, ice-cold chlorosulphonic acid (180 c.c.) (B.D.H. techn.), the temperature being kept below 5°. When the addition was complete (90 minutes), the mixture was poured on 2 kg. of crushed ice, and the oily layer separated, washed, dried, and distilled; it had b. p. 163—165°/15 mm.; yield, 75 g. The sulphonamide, m. p. 115° (Found : N, 6·62. Calc. for $C_{10}H_{13}O_2NS$: N, 6·57%), was obtained quantitatively from the chloride, but the overall yield (84—87%) quoted by Huntress and Autenrieth (*J. Amer. Chem. Soc.*, 1941, **63**, 3446) was not attained.

Substituted Amides.—The amine (2 g.) was shaken with 10% sodium hydroxide (20 c.c.), and *p*-cymenesulphonyl chloride (6 g.) added in one-fifth portions; the mixture was shaken for 5 minutes after each addition. After 15 minutes' boiling and 2 hours' storage, a solid product was obtained, which formed white crystals from ethanol : *p-Cymene-2-sulphonanilide* (*2-methyl-5-isopropylbenzenesulphonanilide*) had m. p. 132·5° (Found : N, 4·90. $C_{16}H_{19}O_2NS$ requires N, 4·84%); the *cyclohexylamide* had m. p. 82° (Found : N, 4·74. $C_{16}H_{25}O_2NS$ requires N, 4·71%), and the *o*-, *m*-, and *p-toluidine* analogues had m. p. 101°, 101·5°, and 129°, respectively (Found : N, 4·7, 4·7, 4·7, respectively. $C_{17}H_{21}O_2NS$ requires N, 4·6%).

Derivatives from benzidine and 4-methyl-1 : 3-phenylenediamine. Benzidine (2·3 g.) or 3-methyl-1 : 4-phenylenediamine (1·5 g.) was shaken with 10% sodium hydroxide (40 c.c.), and the sulphonyl chloride (6 g.) added in one-fifth portions, the mixture being boiled after each addition and finally boiled under reflux for 1 hour and then set aside overnight. The *benzidine* analogue of the above formed grey crystals from *n*-butanol, m. p. 257—258° (Found : N, 7·35. $C_{32}H_{34}O_4N_2S$ requires N, 7·37%), and the *4-methyl-1 : 3-phenylenediamine* derivative formed grey crystals from ethanol (Found : N, 9·10. $C_{17}H_{22}O_2N_2S$ requires N, 8·81%), m. p. 166°. In neither case did further treatment with the sulphonyl chloride raise the m. p.

Morpholine derivative. Morpholine (4·4 g.) was added to a solution of *p*-cymenesulphonyl chloride (6 g.) in benzene (15 c.c.). The morpholine hydrochloride which was immediately precipitated was filtered off, and the benzene removed in a vacuum at 30°. The resultant glass was triturated with light petroleum (b. p. 60—80°) and then recrystallised once from ethanol and twice from light petroleum. The *morpholide* formed white crystals, m. p. 62·5° (Found : N, 5·06. $C_{14}H_{21}O_3NS$ requires N, 4·95%).

Piperidine derivative. Piperidine (2 g.) was shaken with 10% sodium hydroxide (20 c.c.), and *p*-cymenesulphonyl chloride (9 g.) added in one-fifth portions. After being boiled for 30 minutes and kept overnight, the oily product was extracted with ether, and the extract washed and dried (Na_2SO_4). The ether was removed, and the oil distilled in a vacuum. The *piperidide*, b. p. 222—225°/15 mm., was colourless, but could not be induced to crystallise (Found : N, 5·00. $C_{15}H_{23}O_2NS$ requires N, 4·98%).

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Fluorescence and the Beer–Lambert Law. A Note on the Technique of Absorption Spectrophotometry. By E. A. Braude, J. S. Fawcett, and C. J. Timmons.

One of the fundamental principles of quantitative absorption spectrophotometry is the assumption that the intensity of absorption is directly proportional to, and that the extinction coefficient is independent of, the concentration of absorbent (Beer's law) and the length of the absorption path (Lambert's law). As far as we are aware, the validity of Lambert's law has never been questioned. Deviations from Beer's law, on the other hand, are quite frequently encountered, but it appears generally accepted that this is always due to concentration-dependent chemical equilibria such as association or ionisation

reactions. In general, however, simple organic compounds in neutral solution are assumed to obey the Beer–Lambert law, and in many cases the validity of the law has been tested and explicitly confirmed.

We have repeatedly observed (cf. Braude, Fawcett, and Newman, *J.*, 1950, **793**) in the course of work with a wide variety of organic compounds, that the ultra-violet light absorption of substances which exhibit strong fluorescence in solution appears to vary markedly with both concentration and cell length. Moreover, smaller but nevertheless significant deviations from the Beer–Lambert law are found with many compounds which do not exhibit visible fluorescence, and the magnitude of the effects is closely dependent on the type of instrument and the experimental conditions employed. Although none of the compounds concerned would be expected to undergo any reversible reactions in dilute neutral solutions, such an explanation can never be rigidly ruled out for the deviations from Beer's law; the deviations from Lambert's law, on the other hand, which are equally or even more pronounced in these cases, can only be physical in origin. As will be shown in the sequel, it is very probable that the variations of extinction coefficient with concentration are due to the same cause as the variations with cell length, namely to the superposition of transmitted light and scattered fluorescence emission. This phenomenon appears to have escaped notice hitherto and the purpose of this note is to draw attention to the important bearing which it has on the widely employed techniques of absorption spectrophotometry.

Although relatively few quantitative measurements of the fluorescence spectra of organic compounds in solution have been recorded (cf. Haussser, Kuhn, and Kuhn, *Z. physikal. Chem.*, 1935, *B*, **29**, 417; Kortüm and Finckh, *ibid.*, 1942, *B*, **52**, 263; Ley and Specker, *Z. wiss. Photographie*, 1939, **38**, 13; Schoental and Scott, *J.*, 1949, 1683), it is known that unsaturated compounds which exhibit selective ultra-violet or visible-light absorption also give rise to fluorescence emission in the same region. Generally, the fluorescence spectrum is at longer wave-lengths than the absorption spectrum, but in polyatomic compounds some overlap often occurs owing to the close spacing of vibrational levels (cf. Bowen, *Quarterly Reviews*, 1947, **1**, 1). It is clear that if, in absorption measurements, any of the fluorescence emission reaches the recording device, the apparent intensity of transmitted light at that wave-length will be increased, *i.e.* the apparent intensity of absorption reduced, and that the magnitude of this effect will depend on the ratio of the intensities of the recorded fluorescence emission and of the transmitted light. It is necessary to distinguish between two types of instrument, (*a*) those in which the light is dispersed *after* passing through the absorbent (*e.g.* the Hilger Spekker spectrophotometer and most other photographic instruments) and (*b*) those in which the light is dispersed *before* passing through the absorbent (*e.g.* the Beckman and other photoelectric spectrophotometers). In type (*a*) a fraction of the fluorescence emission will be scattered into the slit of the spectrometer and will reach the recording device after dispersion, giving rise to an apparent decrease in absorption intensity at the wave-length of the *fluorescent* light. In this arrangement, the effect will be relatively small (*i.e.* only noticeable with strongly fluorescent substances or bands) and will be spread over the spectrum. It will be larger at high extinctions, when the intensity of real transmitted light is small, but the precise relationship between the extinction coefficient and the concentration and the cell-length may be influenced by at least the following additional factors: (i) decrease of fluorescence intensity at increasing concentrations owing to quenching effects, (ii) change in scattering properties with cell-length and cell shape, and (iii) increasing re-absorption of scattered fluorescence emissions with increasing cell-length. In instruments of type (*b*), the fluorescence emission will be scattered directly into the photoelectric cell, giving rise to an apparent decrease in absorption intensity at the wavelength of the *absorbed* light, and owing to the greater proximity of the cell to the recording device, the effect of the fluorescence emission will be much larger in this type of instrument than in type (*a*). As before, deviations from the Beer–Lambert law will be largest at high extinctions when the intensity of the transmitted light is small. The effect will therefore generally increase with increasing concentration at constant cell-length, and with increasing cell-length at constant concentration, subject to the additional factors mentioned above.

The fluorescence effect is illustrated below by measurements of the highest-intensity bands of naphthalene, anthracene, and styryldimethylcarbinol, using a Beckman photoelectric spectrophotometer (Model DU). Whereas potassium chromate gives concordant intensity values over the whole range of extinctions ($E = 0{\cdot}1$—$2{\cdot}5$) and cell lengths (0·1—1·0 cm.) employed, the apparent extinction coefficients for the organic compounds show startling variations, ε decreasing strongly at high extinctions. The deviations from the Beer–Lambert law generally become appreciable for extinctions above 1·0, and for extinctions higher than 2·0, ε actually decreases with increasing concentration in the case of naphthalene and anthracene. Under these conditions, the intensity of the fluorescent light is evidently greater than that of the transmitted light and therefore the fluorescent intensities in these examples are of the order of one hundredth of the intensity of the incident light. As would be expected, extinction readings in the region where the fluorescence effect is appreciable vary somewhat with the slit width employed. Deviations of a smaller order are also exhibited by the longer-wave-length, lower-intensity bands of napthalene and anthracene. Using a Hilger Spekker photographic spectrophotometer, on the other hand, the Beer–Lambert law is obeyed almost within experimental error ($\pm 2\%$) in agreement with the findings of Mayneord and Roe (*Proc. Roy. Soc.*, 1935, *A*, **152**, 299) and the extinction coefficients correspond fairly closely to the highest values of ε obtained with the photoelectric instrument.

The results obtained with styryldimethylcarbinol show that the fluorescence effect is by no means limited to polycyclic aromatic derivatives (cf. Braude, Fawcett, and Newman, *J.*, 1950, **793**). Since all compounds exhibiting selective absorption in the ultra-violet may theoretically also exhibit fluorescence, deviations from the Beer–Lambert law would indeed be expected to be quite general, but the magnitude of the effect will obviously depend on the wave-lengths and the intensities of the fluorescence bands and little is known at present concerning the dependence of fluorescence on structure in simple unsaturated systems. Using a Beckman instrument, we have observed appreciable deviations from the Beer–Lambert law with other styryl derivatives, but not with benzoic acid or conjugated acyclic dienes.

These findings are of obvious significance in relation to the use of light-absorption data for the characterisation and analysis of organic compounds and in relation to the choice and design of instruments. It is evidently desirable that the Beer–Lambert law should be tested wherever possible

and that the conditions of measurement should be more closely defined than has been the practice hitherto. The extinction range $E = 0{\cdot}3$—$0{\cdot}7$ is usually regarded as instrumentally the most accurate in photoelectric photometry, and the possibility of fluorescence emission provides additional reason for avoiding higher extinctions.

Beckman Photoelectric Spectrophotometer.

c = Concentration in g.-mols./l. l = Cell length in cm. E = Extinction (optical density) reading. ε = Apparent molecular extinction coefficient = E/cl

(i) Potassium chromate in 0·05N-aqueous potassium hydroxide. Maximum at 2725 A.

10^4c	0·285	0·700	2·08	4·87	5·58	3·48				
l	1·0					0·1	0·2	0·33	0·5	1·0
E	0·104	0·251	0·748	1·75	2·38	0·123	0·248	0·423	0·625	1·23
ε	3,660	3,580	3,580	3,540	3,620	3,540	3,560	3,640	3,580	3,620

(ii) Naphthalene in ethanol. Maximum at 2200 A.

10^4c	0·012	0·065	0·15	0·25	0·35	1·55	0·47			
l	1·0						0·1	0·2	0·33	0·5
E	0·119	0·618	1·39	2·05	2·35	2·32	0·518	1·16	1·69	2·28
ε	99,000	95,000	93,000	82,000	67,000	15,000	110,000	108,000	108,000	97,000

(iii) Anthracene in ethanol. Maximum at 2510 A.

10^4c	0·011	0·033	0·055	0·099	0·132	0·154	0·275	0·660	1·38	4·50
l	1·0									
E	0·188	0·565	0·930	1·537	1·805	1·965	2·15	2·22	2·23	2·21
ε	170,000	171,000	170,000	156,000	142,000	128,000	78,500	27,000	16,000	4,900

10^4c	2·75				
l	0·1	0·2	0·33	0·5	1·0
E	0·473	0·933	1·558	1·860	2·05
ε	172,000	170,000	170,000	136,000	74,500

(iv) Styryldimethylcarbinol in 60% aqueous dioxan. Maximum at 2510 A.

10^4c	0·11	0·29	0·55	1·10	4·27	2·14				
l	1·0					0·1	0·2	0·33	0·5	1·0
E	0·212	0·535	0·946	1·53	1·75	0·394	0·738	1·20	1·685	1·74
ε	19,300	18,500	17,200	13,900	4,100	18,400	17,200	16,800	14,800	8,100

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The Dinitrophenylhydrazones of the Halogenobenzaldehydes. By O. L. BRADY and S. G. JARRETT.

WHILE the various halogenobenzaldehydes were available in connection with other work their 2 : 4-dinitrophenylhydrazones have been prepared by addition of the aldehyde (2 g.), dissolved in a small quantity of alcohol, to a hot solution of 2 : 4-dinitrophenylhydrazine sulphate [prepared by the addition of concentrated sulphuric acid (4 c.c.) to a suspension of 2 : 4-dinitrophenylhydrazine (2 g.) in alcohol (50 c.c.)] whereupon the dinitrophenylhydrazones separated. They crystallised from xylene in orange crystals except where otherwise stated. In place of the aldehydes the oximes can be used; as these can be purified by crystallisation, purer products can be obtained from them than from the liquid aldehydes.

$XC_6H_4{\cdot}CH{:}N{\cdot}NH{\cdot}C_6H_3(NO_2)_2$.

X.	M. p.	Found, %. C.	H.	X.	M. p.	Found, %. C.	H.	X.	M. p.	Found, %. C.	H.
o-F	200°	51·8	3·0	*o*-Br	203°	43·2	2·6	*o*-I	215°	38·5	2·2
m-F	266	51·5	2·8	*m*-Br	257	43·1	2·5	*m*-I	258	38·2	2·3
p-F	278	51·2	3·0	*p*-Br	257	42·9	2·8	*p*-I •	258	38·3	2·2
($C_{13}H_9O_4N_4F$ requires C, 51·3; H, 3·0%.)				($C_{13}H_9O_4N_4Br$ requires C, 42·7; H, 2·5%.)				($C_{13}H_9O_4N_4I$ requires C, 37·9; H, 2·2%.)			

• Scarlet crystals.

The dinitrophenylhydrazones of the chlorobenzaldehydes have been described by Blanksma and Wacker (*Rec. Trav. chim.*, 1936, **55**, 658), Ferranti and Bloom (*Amer. J. Pharm.*, 1933, **105**, 381), Eitel and Lock (*Monatsh.*, 1939, **72**, 289), and Graymore and Davies (*J.*, 1945, 293). The melting points of our specimens were: *o*-compound 210° and *m*-compound 255°, which are within 1° of the values given by Blanksma and Wacker but considerably different from those of some other workers. For the *p*-chloro-compound (Found: C, 49·1; H, 2·8. Calc. for $C_{13}H_9O_4N_4Cl$: C, 48·7; H, 2·8%) we find m. p. 266° as compared with 216°, 224°, and 218—220° given by other workers. It seems probable that our compound was an isomeric form like others previously noticed among dinitrophenylhydrazones. It may be noted that the melting points given by other workers for the *p*-compound are between those for the *o*- and *m*-derivatives, which is contrary to general experience with compounds of this type.—THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES, UNIVERSITY COLLEGE, LONDON. [*Received, January 17th*, 1950.]

OBITUARY NOTICE.

SIR WYNDHAM ROWLAND DUNSTAN.

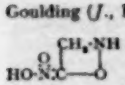
1861—1949.

Sir Wyndham Rowland Dunstan, K.C.M.G., LL.D., F.R.S., died on April 20th, 1949, at the age of 87. He was the son of John Dunstan, Constable and Governor of Chester Castle, and was born at Chester on the 24th May, 1861. He was educated at Bedford School and abroad and began his chemical career at the early age of 18 by becoming assistant to Theophilus Redwood, then Professor of Chemistry at the School of Pharmacy of the Pharmaceutical Society. When this post was divided by the allocation of laboratory work to Professor John Attfield, Dunstan became a demonstrator under Attfield. In 1884 he moved to Oxford having been appointed a demonstrator in the University Chemical Laboratories, and in the following year he was made University Lecturer in Chemistry in Relation to Medicine, a post he retained for some years after succeeding Redwood as Professor of Chemistry in the Pharmaceutical Society's School in 1886. From 1892 to 1900 he was also lecturer in chemistry at St. Thomas's Hospital Medical School, a post he kept for four years after his appointment as Director of the Scientific and Technical Department of the Imperial Institute in 1896. Seven years later he succeeded Sir Frederick Abel in the full Directorship of the Institute, where he remained until his retirement from active work in 1924.

Dunstan's early work was concerned almost wholly with the development of processes for the assay of active components in the natural drugs of the British Pharmacopoeia, and with the application of the results to the production of galenical preparations of these drugs, such as tinctures and extracts, in a standardised form, *i.e.*, containing a specified percentage of the active substance. This was due to the fact that the 1874 Pharmacopoeia was then under revision, Redwood being one of the responsible editors, and the necessary experimental work had to be done in his laboratory. Dunstan had a practical bent of mind well suited to such investigations, as is shown by his work on nux vomica with F. W. Short and on solanaceous drugs with F. Ransom and A. E. Chaston. Nine papers were published on nux vomica of which the most interesting are probably that on the isolation of the crystalline glucoside, loganin, from the pulp of nux vomica fruit (*Pharm. J.*, 1884, [iii], **14**, 1025) and that dealing with the quantitative separation of strychnine and brucine, based on the precipitation of the former as ferrocyanide and recovery of the alkaloid, as adopted in the Pharmacopoeia of 1898. Four papers on the assay of alkaloids in belladonna leaves and root and on the standardisation of their preparations were published by Dunstan and Ransom (*ibid.*, 1884, [iii], **14**, 623; 1884, [iii], **15**, 154; 1885—6, [iii], **16**, 237, 777; 1887, [iii], **17**, 843), and special attention was given to the rhizome of *Scopola carniolica* from which Dunstan and Chaston isolated hyoscyamine, possibly a minute amount of hyoscine, a phytosterol, arachidic acid from the fat, dextrose, and scopoletin (*ibid.*, 1889, [iii], **20**, 461). This drug was at that time regarded as a possible substitute for belladonna, and a group of workers published papers on it: E. M. Holmes on its natural history; T. Greenish on the histology; F. Ransom on its pharmacy; and Sir Dyce Duckworth on the therapeutic action (*ibid.*, pp. 468, 471, 464, 466).

Dunstan also set out to improve the two alkyl nitrite preparations of the Pharmacopoeia and to that end prepared in collaboration with T. S. Dymond, E. J. Woolley, and W. Lloyd Williams (*ibid.*, 1888, [iii], **18**, 861; **19**, 485, 487, 489, 741) the homologous series from methyl to *n*-, *sec.*-, and *tert.*-amyl nitrites, which were examined pharmacologically by Professor J. T. Cash, who, in addition to a number of conclusions which have since become familiar features of pharmacological action in homologous series, showed that the action of the nitrites is not solely, or even mainly in some cases, caused by the amount of nitroxyl (NO_2) they contain, and suggested that the simple nitrites attached themselves more readily to certain constituents of blood and muscle and so acted more quickly, whilst their greater stability ensured longer duration of action (Cash and Dunstan, *Phil. Trans.*, 1893, *B*, **184**, 505). A side issue of this work was the observation by Dunstan and Dymond (*Proc. Chem. Soc.*, 1888, 117; *J.*, 1891, **59**, 410) that the action of alkali on nitroethane produces acetonitrile, nitrous acid, and 3 : 4 : 5-trimethyl*iso*oxazole, the last a type of compound first prepared by Claisen and Lowman (*Ber.*, 1888, **21**, 18, 1149). With nitromethane, alkalis produce, not an *iso*oxazole, but methazonic acid, $C_2H_4O_3N_2$, a substance first obtained by Lecco (*Ber.*, 1876, **9**, 705). It was prepared and examined by Dunstan and

Goulding (*J.*, 1900, **77**, 1262) who, mainly on the ground that on hydrolysis by alkali or acid it produced carbon dioxide, hydroxylamine, and hydrocyanic acid, proposed for it the annexed formula, but shortly afterwards Scholl (*Ber.*, 1901, **34**, 862) suggested that it might be regarded as a nitrogen analogue of acetoacetic acid and formulated as $CH_3{\cdot}NO{\cdot}CH{:}NO{\cdot}OH$, and later Meister (*Ber.*, 1907, **40**, 3435) recorded a number of new reactions for the acid and claimed that it could be represented as $HON{:}CH{\cdot}CH_2{\cdot}NO_2$, or as its conjugated tautomeride $HO{\cdot}N{:}CH{\cdot}CH{:}NO{\cdot}OH$.



About this time the long-continued discussion on the isomerism of aldoximes was beginning and Dunstan and Dymond showed that acetaldoxime, b. p. 114·5°, was a mixture of two forms, one crystalline, m. p. 46·5°, and the other liquid, of which the latter was not obtained quite free from its isomeride. Both were interconvertible and much less stable than the two benzaldoximes but such experimental evidence as could be obtained indicated that they corresponded to the *anti-* and *syn*-aldoximes respectively. Propaldoxime and *iso*butaldoxime were also each separated into *anti-* and *syn*-forms (*J.*, 1892, **61**, 470; *Proc. Chem. Soc.*, 1892, 135; *J.*, 1894, **65**, 206; cf. Carveth, *J. Physical Chem.*, 1898, **2**, 159). In the period 1896—1901, in collaboration with E. Goulding, Dunstan published six papers dealing with the action of alkyl halides on hydroxylamine and on oximes. With the former, action is most complete with methyl iodide, which produces di- and tri-hydroxylamine hydriodides, and trimethylhydroxylamine hydriodide, $(CH_3)_3NO,HI$, later called trimethyloxamine or trimethylamine oxide hydriodide. With ethyl, *n*-propyl, or *iso*propyl iodide only the dialkylhydroxylamine is formed at the first stage but the triethyl compound can be got by further action of the alkyl iodide, though this does not happen with the di-*n*-propyl and di*iso*propyl compounds. These trialkylated substances were the first examples of aliphatic amine oxides, and it was later found that they could be produced by the action of hydrogen peroxide on trialkylamines and that by like means dialkylamines could be converted into the dialkylhydroxylamines $(Alk)_2N{\cdot}OH$, except in the case of dimethylamine, which instead was oxidised to formaldehyde and formic and nitrous acids (*J.*, 1896, **69**, 839; 1899, **75**, 792, 1004; 1901, **79**, 641). Also, with E. Goulding as collaborator, Dunstan investigated the action of alkyl iodides on a series of aldoximes and ketoximes alone and in presence of sodium methoxide in methyl alcohol. In the former case *N*-alkyl derivatives, then represented as alkyl*iso*oximes, *e.g.*, the alkyl*iso*aldoximes $R{\cdot}CH{<}\begin{smallmatrix}O\\|\\NR'\end{smallmatrix}$, were alone formed, whereas in presence of alkali the isomeric ethers, *e.g.*, the alkylaldoximes, $R{\cdot}CH{:}N{\cdot}OR'$, were also produced, the relative proportions of the two isomerides varying with the nature of the oxime and the alkyl iodide used (*J.*, 1897, **71**, 573; 1901, **79**, 628).

Of the remaining investigations probably the most important is that of the aconite alkaloids, on which eighteen papers were published during 1891—1905, with several collaborators, notably W. H. Ince, J. C. Umney, F. W. Passmore, F. H. Carr, H. A. D. Jowett, E. F. Harrison, T. Tickle, H. M. Read, and A. E. Andrews. The early workers on aconitine, Alder Wright in this country and Jurgens in Germany, adopted for the alkaloid the formula $C_{33}H_{45}O_{12}N$ or $C_{32}H_{47}O_{12}N$, and $C_{32}H_{41}O_{12}N$ was found by Dunstan and Ince. Up to that time aconitine had been regarded as benzoylaconine, isomeric with the substance variously named picraconitine, isaconitine, or benzaconine. In 1892 Ehrenburg and Purfurst (*J. pr. Chem.*, 1892, **45**, 604) showed that, when heated dry, aconitine loses acetic acid, and this was later confirmed by Dunstan and Carr (*J.*, 1894, **65**, 176) who isolated and characterised the resulting pyraconitine, $C_{31}H_{41}O_{10}N$. Meanwhile Freund and Beck (*Ber.*, 1894, **27**, 433, 720) had found that the empirical formula of aconitine should be $C_{34}H_{47}O_{11}N$, which after some discussion was accepted by the English workers, and both protagonists agreed that aconitine was acetylbenzoylaconine. It thus became the prototype of the highly toxic diacylaconines characteristic of many aconites of which pseudaconitine from Nepaul aconite was shown to be acetylveratroylpseudaconine (Dunstan and Carr, *J.*, 1897, **71**, 350), indaconitine from *A. chasmanthum* to be acetylbenzoylpseudaconine (Dunstan and Andrews, *J.*, 1905, **87**, 1620), bikhaconitine from *A. spicatum* to be acetylveratroylbikhaconine (Dunstan and Andrews, *ibid.*, p. 1636), and japaconitine from Japanese aconite to be acetylbenzoyljapaconine (Dunstan and Read, *J.*, 1900, **77**, 49). All these alkaloids and certain of their derivatives were examined pharmacologically by Professor Cash, and the detailed results communicated to the Royal Society (Cash and Dunstan, *Phil. Trans.*, 1898, *B*, **190**, 239; 1902, B, **195**, 39, 97; *Proc. Roy. Soc.*, 1905, *B*, **76**, 468; see also Cash, *Brit. Med. J.*, 1908, I, 1213).

The series of papers on "Cyanogenesis in Plants" arose out of the poisoning of domestic animals in Egypt by *Lotus arabicus*, a plant which when fully ripe is collected by the Arabs as fodder for cattle but which had long been known to be poisonous in the early stages of growth.

It was found that dried immature plants when ground and moistened with water produced a strong odour of prussic acid. This cyanogenetic action was traced to the action of an enzyme, lotase, on a glucoside, lotusin, which produced prussic acid, dextrose, and a yellow pigment, lotoflavin (Dunstan and Henry, *Phil. Trans.*, 1901, *B*, **194**, 515). It was not easy in those days to get collected in good condition the considerable supply of material required for chemical examination and though a fair quantity of this plant became available it arrived in small quantities, in which the yield of prussic acid varied, and the plant was sometimes mature enough to yield only traces. The total amount of lotusin obtained was small in comparison with the yield of prussic acid from dried young plants in good condition, and this deficiency is still not accounted for in the preliminary account of a re-examination of the plant started just before the outbreak of war (Henry, *J. Soc. Chem. Ind.*, 1938, **57**, 248), in which a well-defined pigment glucoside, $C_{33}H_{44}O_{11}$, was isolated along with the cyanogenetic glucoside, lotaustralin, which Finnemore, Cooper, and Stanley (*ibid.*, p. 162) first obtained about the same time from the related plant *Lotus australis* var. *pubescens*. In this second investigation in which acetone was used as the extracting medium in place of alcohol, no lotusin was isolated but the residual extracts still contained much cyanogenetic material. The second plant examined was " dhurra " (*Sorghum vulgare*) from Egypt. In this case also the toxic substance disappears as the plant matures and there is none in the seed, which is a common tropical food-grain. The cyanogenetic glucoside in this case was named " dhurrin " and proved to be a glucoside of *p*-hydroxybenzaldehyde cyanohydrin. An easier material to deal with was the seeds of *Phaseolus lunatus*, which as collected from the semi-cultivated plant, grown as a green manure in Mauritius, are brown with violet patches and poisonous, as distinct from the white and harmless " Lima beans," yielded by the carefully cultivated plant. Previous observations by Bonamé in Mauritius and by van Romburgh in Java had shown that this plant when crushed, moistened with water, and distilled yielded acetone and prussic acid. The formation of these products was traced to the action of an enzyme on phaseolunatin, which proved to be a glucoside of acetone cyanohydrin (Dunstan and Henry, *Proc. Roy. Soc.*, 1903, *B*, **72**, 285) which was later also isolated from cassava root and from young flax plants (Dunstan, Henry, and Auld, *Proc. Roy. Soc.*, 1906, *B*, **78**, 145, 152; 1907, **79**, 315), and the linamarin obtained from flax by Jorissen and Hairs (*Bull. Acad. Roy. Belg.*, 1891, [iii], **21**, 529) was shown to be identical with phaseolunatin.

Among other natural products examined mention may be made of the Egyptian plant *Hyoscyamus muticus*, which was shown to contain hyoscyamine without hyoscine (Dunstan and Brown, *J.*, 1899, **75**, 72) and has now for many years been a commercial source of atropine.

Dunstan also made an excursion into inorganic chemistry in a group of papers on the rusting of iron, in which he maintained that the essential condition for the aerial oxidation or rusting of iron and other metals is the simultaneous presence of oxygen and liquid water, that carbon dioxide facilitates but does not initiate the process, and that agents such as alkalis, potassium dichromate, sodium nitrite, and potassium ferrocyanide, which prevented, to a greater or less extent, the formation of rust were also agents in whose presence the decomposition of hydrogen peroxide occurs, from which he deduced that hydrogen peroxide is an essential intermediary in the formation of rust and that in the case of iron the process may be represented :

$$Fe + O_2 + H_2O = FeO + H_2O_2; \quad 2FeO + H_2O_2 = Fe_2O_3(OH)_2.$$

Though this view (*Proc. Chem. Soc.*, 1903, **19**, 150) was supported by much experimental evidence (Dunstan, Jowett, and Goulding, *J.*, 1905, **93**, 1548) it led to considerable discussion. Up to that time the findings of Grace Calvert (*Manchester Lit. Phil. Mem.*, 1871, **5**, 104) as interpreted by Crum Brown (*J. Iron Steel Inst.*, 1888, 129), that rusting was due to the combined action of the carbon dioxide and oxygen of the air, had not been questioned and it was assumed that the iron carbonate first formed was gradually converted into a ferric hydroxide or rust by the further action of atmospheric oxygen. That theory was now supported by G. T. Moody and his notes led to interesting discussions at meetings of the Society (*Proc. Chem. Soc.*, 1903, **19**, 157, 239, 273; 1906, **22**, 101; 1907, **23**, 84; 1909, **25**, 34; *J.*, 1906, **89**, 720; cf. Dunstan, *Proc. Chem. Soc.*, 1907, **23**, 63). An electrolytic explanation of the corrosion of iron was advanced by Whitney (*J. Amer. Chem. Soc.*, 1903, **25**, 394) and received some support from Walker, Cederholm, and Beut in the United States (*ibid.*, 1907, **29**, 1251) and from Tilden in this country (*J.*, 1908, **93**, 1356). Experimental evidence against both these theories was provided by Dunstan *et al.* (*loc. cit.*) and, in returning to the subject, Dunstan and J. R. Hill (*J.*, 1911, **99**, 1835, 1853) emphasised that " none of the existing theories adequately explains how the various inhibiting agents prevent rusting " and in the first of the two papers quoted they record the results of a number of new experiments showing that all these inhibitors act by rendering iron

" passive " and that this passivity persists after removal of the iron from the solution causing it. It was also suggested that, as potassium iodide and certain other reducing agents destroy hydrogen peroxide and yet do not inhibit rusting, the peroxide is probably not an intermediate product of the main reaction as originally postulated but may be the result of a secondary reaction, since oxidation can apparently proceed without its formation, and they conclude that " metals undergo aerial oxidation by direct action of oxygen dissolved in water."

In 1899, largely under Dunstan's influence, a Research Laboratory was inaugurated by the Pharmaceutical Society, by addition to their premises in Bloomsbury Square, and most of the work referred to above was started in that institution and was transferred to, and continued in, the Scientific and Technical Department of the Imperial Institute when Dunstan moved there in 1896. The Institute was founded to commemorate the fiftieth year (1887) of Queen Victoria's reign and was opened by Her Majesty in 1893, by which time some progress had been made in installing in the Public Exhibition Galleries representative collections of the natural products of the Colonies and India, and it was possible to begin giving attention to the second objective of the Institute, the scientific examination of new or little known products from the Overseas Empire. The Institute was severely handicapped by lack of funds but the first Director, Sir Frederick Abel, found it possible to secure the co-operation of a number of eminent men of science, who undertook to examine in their own laboratories materials provided by the Institute. Much useful work was done under this arrangement, *e.g.*, by Dr. A. W. Crossley and Mr. Le Sueur on Indian vegetable oils, by Professor W. C. Unwin on mechanical tests of new timbers, by Professor A. H. Church on the composition of Indian food-grains, by Messrs. Cross and Bevan on new fibres, and by Professors A. G. Perkin and J. J. Hummel respectively on the components and the tinctorial properties of Indian dye-stuffs. This arrangement was continued when, thanks to the generous financial help provided by the Commissioners of the 1851 Exhibition, the Goldsmiths' and Salters' Companies and other donors, it was possible to equip and operate the laboratories of the Scientific and Technical Department on Dunstan's assumption of the Directorship in 1896. During the first few years it was still possible to carry on mainly detailed investigations such as those already referred to, but as the facilities offered by the Institute for the examination of natural products became better known in the Colonies and India, thanks to Dunstan's organizing ability and driving power, the character of the work done had perforce to change, as will be seen in the volume of " Technical Reports and Scientific Papers " published by the Imperial Institute in 1903, which opens with an interesting preface by Sir Frederick Abel describing the inception of the Institute and the objectives which its founders had in view. Part I of the volume is a series of reports on coals, iron ores, mica, and other minerals, followed by collected reports on fibres, edible and essential oils and oil-seeds, rubber and gutta percha, gums and resins, medicinal plants and tobacco, tanning and dyeing materials, fodder plants and food-grains, and timbers, many of the items being provided by the scheme of co-operation with the external expert referees referred to above. From 1903 the more important technical reports of the Department were published in the quarterly *Bulletin of the Imperial Institute* but in the period 1909—1914 a further group of five collected reports, with Dunstan as responsible editor and dealing with Fibres, Gums and Resins, Foodstuffs, Rubber and Gutta Percha, and Oil-seeds, Oils, Fats, and Waxes, was issued in the Miscellaneous Series of Colonial Reports. Also printed in this series was the " Report on British Cotton Cultivation," which with Dunstan's prior " Report to the Board Trade on Cotton Cultivation in the British Empire and Egypt " (1904) indicates the part played by the Imperial Institute, when, in the early years of this century, there was a prospective shortage of raw cotton and strenuous efforts were made to increase cultivation of this commodity within the Empire. In the same connection Dunstan also paid official visits to Cyprus and Asia Minor and prepared reports, published in the same series, on the agricultural resources of those areas with special reference to cotton cultivation. He was also responsible for another important development in the exploration and utilisation of Colonial natural resources, *viz.*, the institution of Mineral Surveys in Ceylon, Southern Nigeria, Northern Nigeria, and Nyasaland. These were conducted by geological surveyors operating in the territories named, and the mineral samples collected by them were sent to the Imperial Institute for mineralogical and chemical examination. Reports on this work were also published in the Miscellaneous Series of Colonial Reports. Among the more interesting results were the discovery of thorium minerals, especially the new mineral thorianite (Dunstan, *Nature*, 1904, **69** 510; with G. S. Blake, *Proc. Roy. Soc.*, 1905, *A*, **76**, 253; with B. M. Jones, *ibid.*, 1906, *A*, **77**, 346) in Ceylon by Dr. Coomaraswamy, the location of beds of lignite and of the now important Udi coalfield in Southern Nigeria by Mr. A. E. (later Sir Albert) Kitson, and of deposits of iron ore in Northern Nigeria by Dr. J. D. Falconer who subsequently became Director of the Geological

Survey of Nigeria and is the author of a monograph on "The Geology and Geography of Northern Nigeria."

Dunstan also considered the publication of information regarding the natural resources of the Overseas Empire as an important function of the Imperial Institute, and a section of the quarterly *Bulletin* was always allocated for this purpose. This also was the idea behind three series of publications issued by Mr. John Murray, namely:

"The Imperial Institute Handbooks to the Commercial Resources of the Tropics," of which four volumes were issued with Dunstan as Editor.

"The Imperial Institute Monographs on Mineral Resources with special reference to the British Empire." Fifteen of these, each dealing with one set of minerals, were prepared under the direction of the Mineral Resources Committee of the Imperial Institute.

A series of reports on rice, lac, turpentine, oil-seeds, etc., resulting from the Indian Trade Enquiry authorised by the Secretary of State for India in 1916.

The *Bulletin of the Imperial Institute* for 1923 contains a long and detailed "Report on the Operation of the Imperial Institute," which deals with the organization and work of the Institute up to a date shortly before Dunstan's retirement. It is an interesting account of the foundation and progress of an organisation concerned with this important phase of colonial economic development, to which he devoted nearly two-thirds of his working life.

Dunstan was a Fellow of the Chemical Society for 70 years, having joined in 1879; he served on the Council in 1889 to 1891 and was Secretary from 1893 to 1903 and a Vice-President from 1904 to 1906. He became a Fellow of the Royal Society in 1893 and was a member of the Council from 1905 to 1907. He presided over the Chemical Section of the British Association at the meeting held in York in 1906. In 1910 he became President of the International Association of Tropical Agriculture, which had its headquarters in Paris, and in that capacity was President of the Third International Congress of Tropical Agriculture, held at the Imperial Institute in 1914, just before the outbreak of the First World War. He also served on the Council of the Royal Geographical Society in 1916. Dunstan was fond of travel. As already mentioned he visited Cyprus in 1904 and Asia Minor in 1907 at the request of the Colonial Office and, at the invitation of the respective governments, he undertook similar missions to Ceylon in 1910 and 1914, India in 1914, and Newfoundland in the same year.

Dunstan was an excellent lecturer and in his teaching days was always popular with his students. He was interested in education, especially in science teaching, and this led to his service as Secretary of the British Association Committee dealing with that subject from 1887 to 1891. It was also no doubt this interest which led to his serving at various times on the governing bodies of constituent colleges of London University and to his becoming a Vice-President of the Girls' Public Day School Trust.

Dunstan was also concerned with philosophy and in an article on "Our Quest for Philosophy and what came of it," contributed to the *Hibbert Journal* for July 1942, he describes his association with Dr. Alfred Senier in the foundation of the Aristotelian Society of which he was one of the first three Vice-Presidents, and for a time he edited the Society's *Proceedings*.

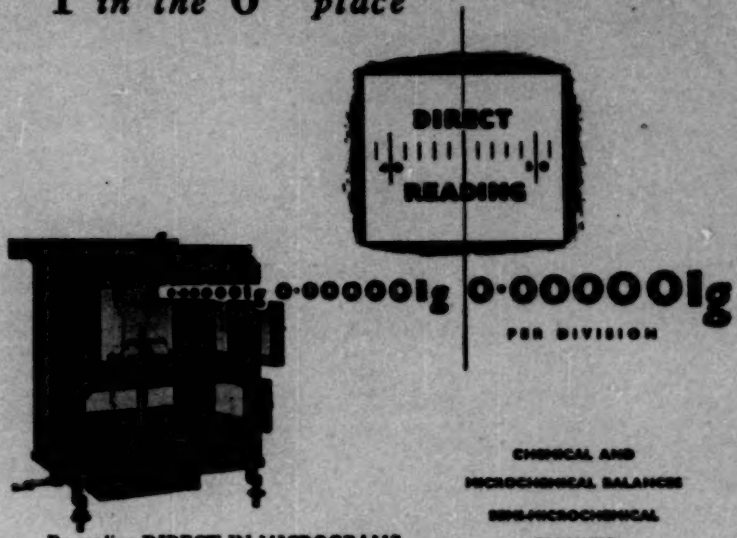
He was also an honorary member of the Institut Egyptien, and a Commander of the Order of Leopold of Belgium.

He was made C.M.G. in 1913 and K.C.M.G. on his retirement in 1924.

Dunstan was married twice, in 1886 to Emilie Fordyce Maclean, who died in 1893 leaving a son and a daughter, and in 1900 to Violet Hanbury-Tracy, who survives him with a second daughter.

T. A. Henry.

"1 *in the* 6*th place*"



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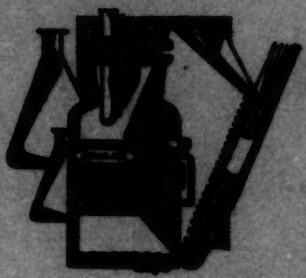

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APRIL, 1950